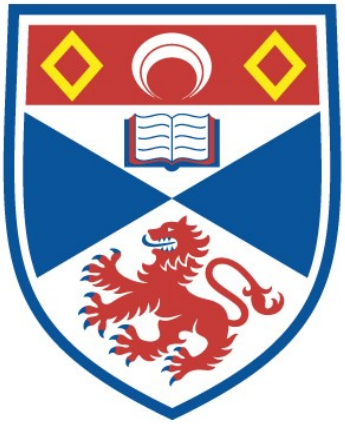
PYRAZOLIDINONES AS TEMPLATES IN ASYMMETRIC CATALYSIS

Eoin Gould

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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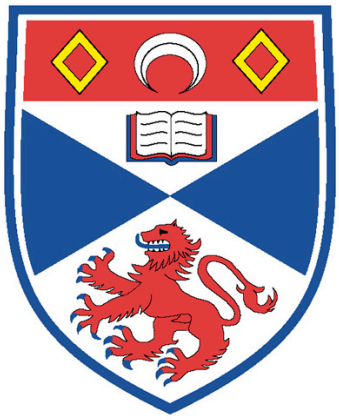

University
of
St Andrews

Pyrazolidinones as Templates in Asymmetric Catalysis

Eoin Gould

Thesis submitted in partial fulfillment for the degree of Doctor of Philosophy

April 2012

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Abstract

This thesis principally focuses on the development of a novel series of asymmetric iminium ion organocatalysts, based on the pyrazolidin-3-one template. Also described is the development of a novel asymmetric Steglich rearrangement with pyrazolyl carbonates.

The pyrazolidin-3-one framework has been identified as a potentially effective new scaffold for iminium ion organocatalysis. The development of a synthetic route to racemic pyrazolidinone catalysts is outlined which allows for systematic variation of key substituents. The influence of these groups on reactivity and diastereoselectivity in the Diels-Alder reaction of (*E*)-cinnamaldehyde and cyclopentadiene is described and an optimised catalyst identified.

A method for the resolution of a simple pyrazolidinone precursor was then investigated in order to access an enantioenriched catalyst for asymmetric reaction. Resolution was achieved by amide coupling to a chiral acid, chromatography to separate the subsequent diastereoisomers and acid cleavage. The initial enantioenriched catalyst gave modest enantioselectivity in the Diels-Alder reaction.

The diastereoisomeric intermediates in the resolution process were themselves identified as active and enantioselective iminium ion organocatalysts. In general, one diastereoisomer was superior in terms of enantioselectivity, indicating a 'matching' of the two catalyst stereocentres. An optimised asymmetric diastereoisomeric catalyst derived from a trifluoromethyl-substituted pyrazolidinone and Cbz-protected proline gave good diastereo- and enantioselectivities in Diels-Alder reactions with a range of aryl aldehydes. Mechanistic investigations with this compound then found that fast ring-opening occurs under catalysis conditions creating a new chiral hydrazide which was catalytically active at catalyst loadings as low as 1 mol%.

Also explored was the Steglich rearrangement of structurally related pyrazolyl carbonates. Rearrangement was observed with a range of Lewis base organocatalysts, with N-heterocyclic carbenes (NHCs) generally superior. Chiral NHCs were also effective in an asymmetric reaction, particularly with methyl substituted pyrazolyl carbonates.

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Abbreviations

A	Arrhenius parameter
app	apparent
aq	aqueous
Ar	aryl
Boc	*tert*-butoxycarbonyl
BOP	(benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate
Bn	benzyl
br	broad
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
CI	chemical ionisation
cm^{-1}	wavenumbers
d	doublet/ deuterated
DBN	1,5-diazabicyclo[4.2.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereoisomeric excess
DHPB	3,4-dihydro-2*H*-pyrimido [2,1-*b*] benzothiazole
DMAP	dimethylaminopyridine
DMF	*N,N*,-dimethylformamide
DMSO	dimethylsulfoxide
E_a	activation energy
EDCI	*N*-(3-dimelhylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
eq	equivalent (stoichiometric)
ESI	electrospray ionisation
Et	ethyl
g	gram(s)
GC	gas chromatography
h	hour(s)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HMBC	heteronuclear multiple-bond correlation
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
k	rate constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium di-*iso*-propylamide
lit.	literature
LUMO	lowest unoccupied molecular orbital
M	molar (i.e. mol dm^{-3})
m	multiplet
Me	methyl
Mes	mesityl
mg	milligrams
min	minute(s)
mL	millitre(s)
mp	melting point
MS	mass spectrometry
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
oct	octet
Ph	phenyl
ppm	parts per million
PPY	4-pyrrolidinopyridine
i-Pr	*iso*-propyl
PyBOP	(benzotriazol-1-yloxy)tripyrrolidino-phosphonium hexafluorophosphate
q	quartet
quin	quintet
rt	room temperature
s	singlet
sept	septuplet
sext	sextuplet
S_N2	substitution, nucleophilic, bimolecular
t	triplet
$t^{1/2}$	time to reach 50 % conversion
TADDOL	(4*R*,5*R*)-2,2-dimethyl-*α,α,α′,α′*-tetraphenyldioxolane-4,5-dimethanol
TBS	tetrabutlysilyl
Tf	trifluoromethanesulfonyl
TMS	*tert*-butyldimethylsilyl
t_R	retention time
Ts	*p*-toluenesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography

Chapter 1: Introduction

This chapter outlines the rationale and literature precedent behind the development of a new series of iminium ion organocatalysts based on a pyrazolidin-3-one core. The concept of organocatalysis and its subfields are discussed, with particular emphasis on enamine and iminium ion catalysis. The Diels-Alder reaction, commonly employed as a model reaction for novel iminium catalysed processes, is introduced and a selection of modern activation methods outlined. Pyrazolidin-3-ones and some recent applications of such compounds as substrates are then discussed followed by a rationale of their potential as catalysts, supported by related literature examples.

1.1 Organocatalysis

The area of organocatalysis continues to draw great interest from the synthetic research community since the term was popularised by MacMillan in 2000,[1] although many reports concerning the use of organic molecules as catalysts pre-date this. Organocatalysis can be defined as the use of substoichiometric amounts of an organic molecule, that does not contain a metal atom, in order to accelerate chemical reactions.[2] Enzymes, many of which are composed entirely of amino acid chains, are excellent examples of such an approach. Such molecules are capable of catalysing specific reactions with high yields and enantioselectivity.[3] The absence of any metal atoms in organocatalysis may provide several advantages over conventional catalytic methods. Many metals useful for catalysis, such as palladium, have a low natural abundance and are therefore costly to obtain. These metals are often toxic and their inclusion in a catalyst leads to a complex with high molecular weight. In addition, organocatalytic reactions are generally tolerant of air and water and easy to perform.[4]

The term organocatalysis covers a large spectrum of different reactions and this area has been extensively reviewed.[3,4,5] Methods of organocatalytic activation can be broadly classified as Brønsted acid, Brønsted base, Lewis acid and Lewis base catalysis (Figure 1.1).[3]

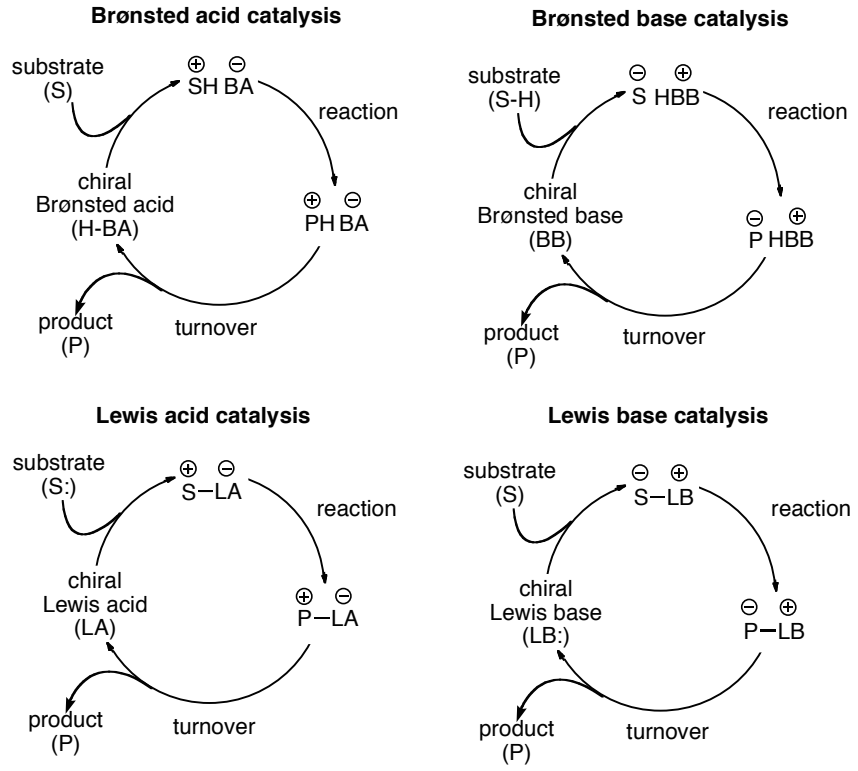


Figure 1.1: Simplified organocatalytic cycles.

This review will be primarily focused on Lewis base catalysis, in particular iminium ion activation. A brief overview of the other major sub-divisions of organocatalysis are outlined in the following sections.

1.1.1 Brønsted acid catalysis

Brønsted acid catalysis simplistically involves initial proton transfer to an acceptor molecule that is then activated to further chemistry.[6] The majority of Brønsted acid catalysts contain either a urea, thiourea or phosphoric acid moiety.[7] More recent studies have also found that carboxylic acids can be employed, as in the report of Maruoka *et al.* on the use of di-acid **3** for the addition of diazoacetates to Boc-protected imines (Figure 1.2).[8] Proton transfer to imine **1** accelerates addition of the nucleophile with the chiral anion controlling the face of attack to give products in high ee (95 % for the given example). Subsequent publications have significantly extended this methodology through the use of *in situ* generated azomethine imines.[9]

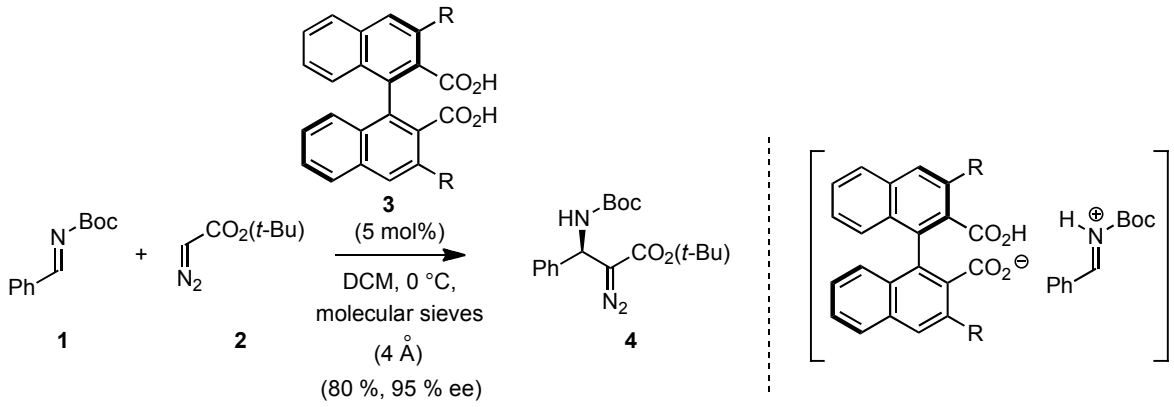


Figure 1.2: Brønsted acid catalysed addition of diazoacetate **2** to imine **1** (R = 2,6-dimethyl, 4-*tert*-butylphenyl)

1.1.2 Brønsted base catalysis

One of the first examples of chiral organic Brønsted base catalysis, where the first step is activation of the substrate by deprotonation, was described by Wynberg and Helder in 1975 with the conjugate addition of nitrosulfones to α,β-unsaturated ketones using quinine.[10] Recent developments have frequently focused on the use of bifunctional catalysts that activate both nucleophiles and electrophiles to enhance and control bond-forming processes.[11] A recent example comes from Connon and co-workers who described the conjugate addition of malonates to nitroalkenes catalysed by a cinchona alkaloid modified to include a thiourea unit (Figure 1.3).[12] The quinuclidine tertiary amine acts as the Brønsted base to activate dimethyl malonate **6** and the thiourea activates the nitroalkene **5** by hydrogen bonding. **8** is derived from the C(9)-epimer of the naturally occurring alkaloid but performed substantially better than the parent alkaloid and gave addition products with excellent enantioselectivities. The activity of the catalyst was such that loading could be taken down to as little as 0.5 mol% in the example in Figure 1.3.

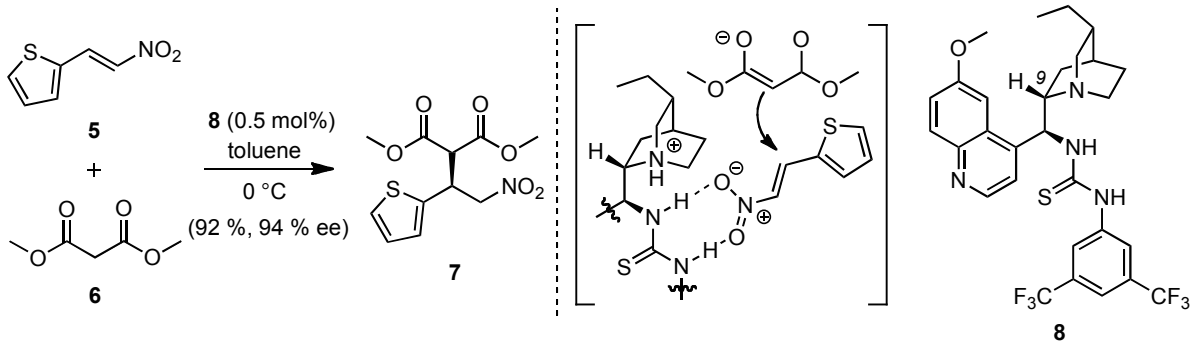


Figure 1.3: Addition of **5** to **6** catalysed by **8**

1.1.3 Lewis acid catalysis

Lewis acid catalysis proceeds by the activation of a substrate by electron donation to a catalyst.[13] An organocatalytic example was reported by Kočovský *et al.* (Figure 1.4).[14] Chloride displacement from allylsilane **10** by *N*-oxide catalyst **11** creates a Lewis acidic intermediate that activates and orientates benzaldehyde **9** *cis* to the allyl unit, as shown. This cyclic transition state then provides (*S*)-allyl alcohol **12** in high ee. Inclusion of tetrabutylammonium chloride increased both reaction rate and enantioselectivity.

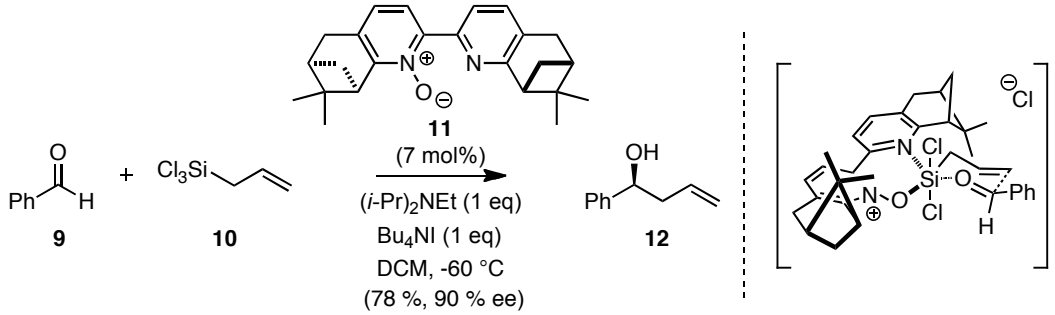


Figure 1.4: Sakuri-Hosomi-type allylation catalysed by chiral *N*-oxide **11**

1.1.4 Lewis base catalysis

Lewis base catalysis represents the largest of the subfields within organocatalysis.[15] One of the key reasons for this is the wide range of different reactive intermediates which fall into this category, these include N-heterocyclic carbene, ammonium enolate, acyl-ammonium and sulfur ylide catalysis.[3] However, this chapter focuses on the two related subfields of enamine and iminium ion catalysis, which utilise amines to promote reactivity. These two areas share a common substrate activation pathway, as shown in Figure 1.5. Condensation of a secondary amine with a carbonyl group leads to an iminium ion. If this species contains a suitable enolisable proton on the α-carbon, deprotonation can generate an enamine. The formation of the enamine significantly alters the reactivity in relation to the starting carbonyl, making the compound nucleophilic at the α-carbon.

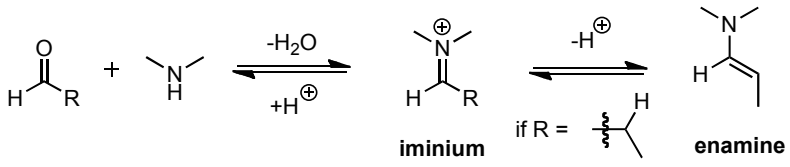


Figure 1.5: Reactive species of iminium ion and enamine catalysis

1.1.4.1 Enamine catalysis

An early example of enamine catalysis is the Hajos-Parrish-Eder-Sauer-Wiechert reaction, reported in the early 1970's.[16] This intramolecular aldol reaction yields bicyclic alcohol **18**, a useful intermediate in steroid synthesis, from triketone **13** (Figure 1.6). The reaction is catalysed by the amino acid (*S*)-proline **14** in high yield and enantioselectivity. It is proposed that condensation of (*S*)-proline **14** with triketone **13** leads to enamine intermediate **15**. The high stereocontrol observed in this reaction can be rationalised by it proceeding through a highly ordered six-membered ring transition state **16**.[17] The hydrogen-bond interaction between the ketone and the stereodirecting carboxylic acid leads to preferential formation of one enantiomer of the product **18**, after hydrolysis of iminium ion intermediate **17**.

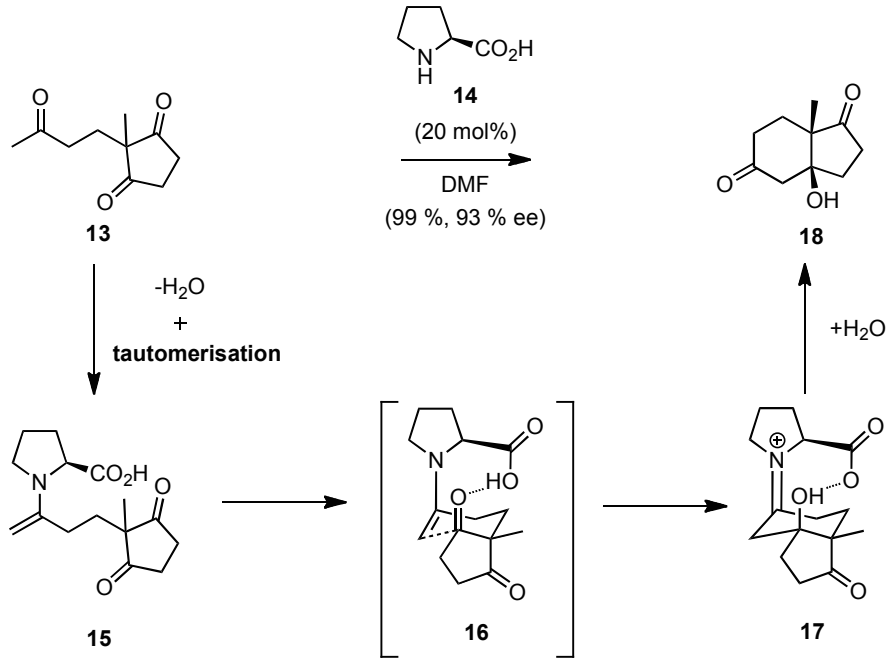
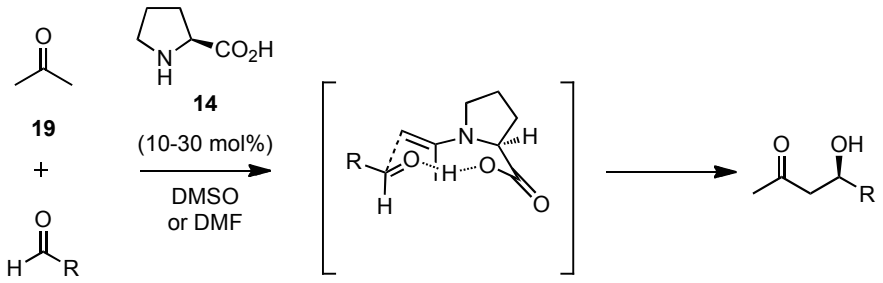


Figure 1.6: Hajos-Parrish-Eder-Sauer-Wiechert reaction

In one of the first examples of 'modern' organocatalysis, the intermolecular variant of this reaction, between acetone **19** and a small range of aldehydes, was reported.[18,19] (*S*)-Proline **14** is again used as the catalyst (Table 1.1). Competing side reactions, such as self-aldolisation, are suppressed by the use of an excess of acetone **19** (20 % by volume). Notably, yield and enantioselectivities are heavily dependent on the nature of the aldehyde substrate. For example, use of benzaldehyde gave aldol product in 62 % yield with a 72 % ee (entry 1). However, α-branched aliphatic aldehydes (entries 2 and 3) each gave their respective aldol products in greater than 80 % yield and greater than 95 % ee. The high enantioselectivity observed in these reactions has been rationalised by the reaction proceeding *via* the cyclic transition state shown

in Table 1.1. In this model, preferential approach of the aldehyde to the enamine is controlled by hydrogen-bonding between the aldehyde carbonyl and the carboxylic acid of the enamine. This mode of activation has been widely expanded to other processes including Mannich[20] and amination reactions.[21]



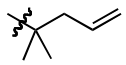
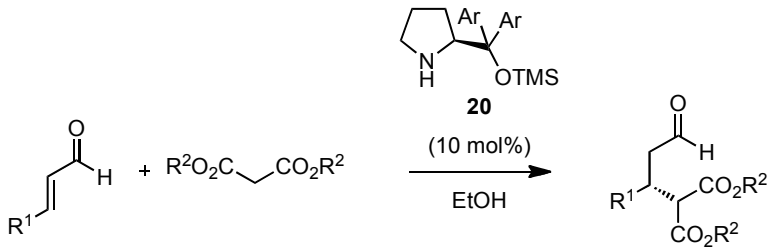
Entry	R	Yield (%)	% ee
1		62	72
2		97	96
3		85	>99

Table 1.1: Aldol reaction catalysed by (*S*)-proline **14**

1.1.4.2 Iminium ion catalysis

Enamines are formed from deprotonation of an intermediate iminium ion species but iminium ions themselves can also be used as reactive intermediates. Formation of an iminium ion from a carbonyl group generates a molecule with a lower LUMO energy, relative to the starting carbonyl. This increases the electrophilic nature of the carbonyl group and has an orthogonal influence to enamine formation, which converts the carbonyl into a nucleophile. Iminium ion catalysis has proven to be one of the most fruitful areas of organocatalysis research and has been applied to a range of reactions such as Friedel-Crafts alkylation and Michael reactions.[22] For example, conjugate addition of methyl or benzyl malonates to β-aryl, α,β-unsaturated aldehydes can be catalysed by (*S*)-proline derived amine **20** (Table 1.2).[23] In this protocol, the reaction of (*E*)-cinnamaldehyde with dimethyl malonate (entry 1) gives an 85 % yield of Michael addition product with high enantioselectivity (94 % ee). A range of β-aryl, α,β-unsaturated aldehydes are tolerated, with reactions normally proceeding with good yield and high enantioselectivity.



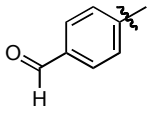
Entry	R^1	R^2	Yield (%)	% ee
1		Me	85	94
2		Bn	95	86
3		Bn	83	92

Table 1.2: Organocatalytic conjugate addition of malonates to α,β-unsaturated aldehydes (Ar = 3,5-$(CF_3)_2$-C_6H_4)

It is believed that reaction proceeds through the iminium ion intermediate shown in Figure 1.7.[24] Minimisation of steric interactions between the stereodirecting group and the olefinic substituent leads to preferential formation of the (*E*)-isomer of iminium ion **B**. Preferential addition of the malonate *anti* to the stereodirecting group leads to the configuration observed in the products.

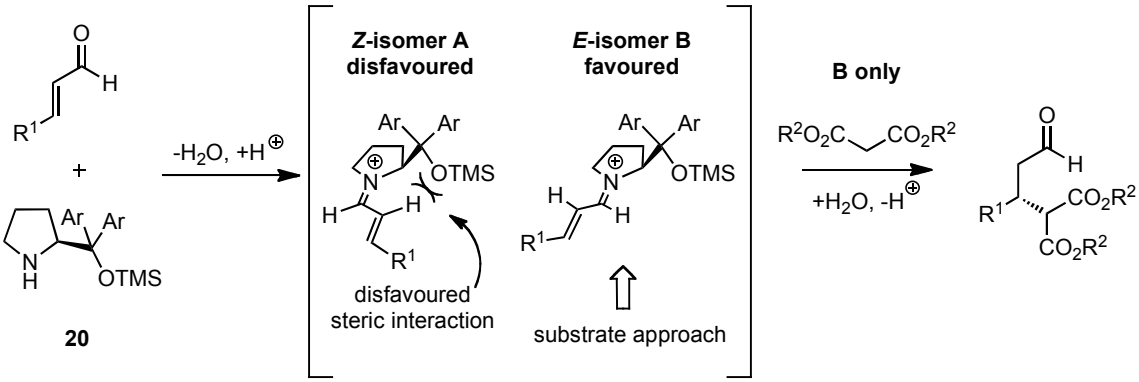


Figure 1.7: Potential geometries of iminium ion intermediates derived from catalyst **20** (Ar = 3,5-$(CF_3)_2$-C_6H_4)

1.2 The Diels-Alder cycloaddition

The Diels-Alder reaction is a [4+2] cycloaddition of a diene and a dienophile wherein two new carbon-carbon bonds are formed in a concerted manner.[25,26] The reaction has found great synthetic utility because it enables rapid access to highly useful cyclohexene-type structures. Furthermore, it can potentially lead to the formation of up to four new stereocentres in a controlled manner.[22] The reaction produces two diastereoisomeric products that can be

classified as either *exo* or *endo*. There has been a great deal of research into methods to achieve rate acceleration and induce asymmetry in such reactions, such as molecular recognition,[27] Lewis acid catalysis[25,28] and a number of organocatalytic approaches.[2,3,22] Examples of each of these methods are described in the following sections.

1.2.1 Molecular recognition

In an example of molecular recognition, the reaction between furan **21** and maleimide **22a** resulted in only 4 % conversion to product in 5 hours (Figure 1.8).[29] The product was produced as a mixture of diastereoisomers, ***exo-*** and ***endo*-23a**, in a ratio of 2:1, respectively. A significant rate acceleration was observed in the reaction of **21** with **22b**, where the ester group has been replaced with a carboxylic acid, with 80 % conversion in the same time. Additionally, only the *exo*-adduct ***exo*-23b** was observed in this case.

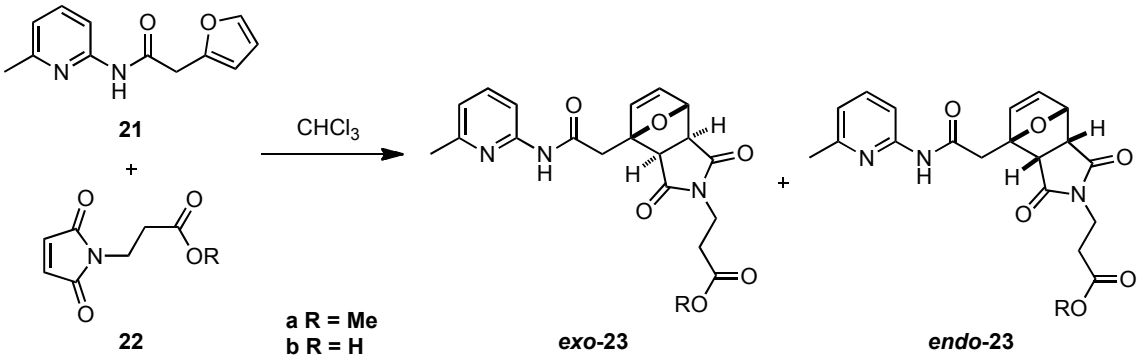


Figure 1.8: Recognition mediated Diels-Alder cycloaddition

Furan **21** and maleimide **22b** have been designed with complementary recognition sites on their respective side chains (Figure 1.9). These hydrogen-bond interactions bring the reactants together and orientates them for reaction thereby providing a rate acceleration relative to the unmediated model system of **21** and **22a**.

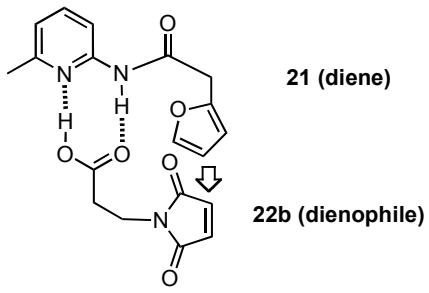


Figure 1.9: Molecular recognition of furan **21** maleimide **22b**

1.2.2 Lewis acid catalysis

A range of Lewis acids, such as aluminium trichloride, are capable of catalysing Diels-Alder cycloadditions (Figure 1.10).[25] In the reaction of anthracene **25** with dimethyl fumarate **24**, the uncatalysed reaction requires a temperature of 101 ºC for 3 days to give full conversion to **26**.[30] The introduction of aluminium trichloride gives complete conversion in 2 h at room temperature. The coordination of the Lewis acid to the carbonyl of the electron-deficient dienophile **24** lowers the LUMO energy relative to the uncoordinated olefin, bringing it closer to the HOMO energy of the electron-rich anthracene **25**. By reducing this energy gap, addition is accelerated, leading to an increase in reaction rate.

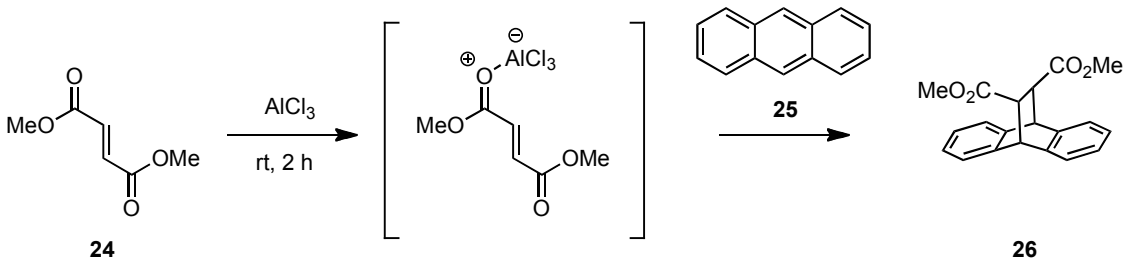


Figure 1.10: Lewis acid catalysed Diels-Alder cycloaddition of anthracene **25** with dimethyl fumarate **24**

Chiral Lewis acids, such as **29**, have been developed that promote enantioselective Diels-Alder cycloadditions (Figure 1.11).[31] In the example below, the chiral diazaaluminolidine **29** catalyses the addition of diene **27** to **28** to give only the *endo* diastereoisomer of acryloyl oxazolidinone **30** in 93 % yield and with 96 % ee. It has been noted as a general feature of Lewis acid-catalysed Diels-Alder reactions that, of the two possible diastereoisomers, the *endo* diastereoisomer is usually favoured.[32]

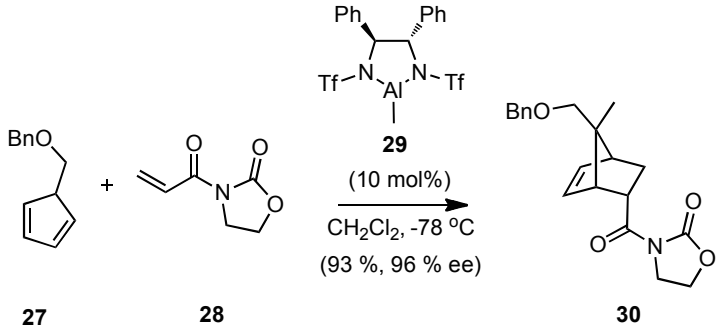


Figure 1.11: Diels-Alder reaction catalysed by chiral diazaaluminolidine **29**

1.2.3 Organocatalysis

Organic Brønsted acids can achieve the same LUMO-lowering effects as Lewis acid catalysis *via* hydrogen-bonding interactions with the dienophile and enantioselective variations utilising this activation mode have been developed.[6,33] An example is shown in Scheme 1.12 where

TADDOL derivative **33** catalyses the reaction of amino siloxydiene **31** with methacrylaldehyde **32** to give Diels-Alder adduct **34**, which was not isolated (Figure 1.12).[34] Instead, reduction and desilylation gave the cyclohexenone **35** in 91 % ee and 83 % total yield over the 3 steps.

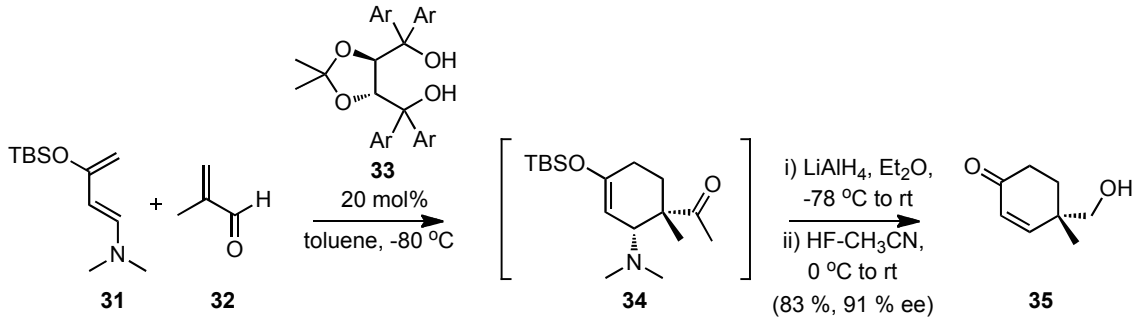
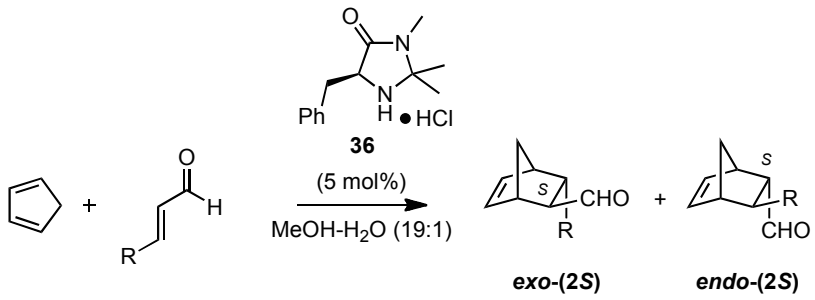


Figure 1.12: Diels-Alder reaction catalyst by TADDOL derivative **33** (Ar = 1-naphtyl)

1.2.3.1 MacMillans imidazolidinones

In 2000, MacMillan *et al.* postulated that a similar LUMO-lowering effect could be achieved using iminium ion catalysis.[1] Computational studies led to the design of imidazolidinone catalyst **36**, which successfully catalysed the cycloaddition of a small range of both aliphatic (entry 1) and aryl (entries 2 and 3) α,β-unsaturated aldehydes with cyclopentadiene (Table 1.3). Reactions proceeded with high yield and excellent levels of enantioselectivity, though little diastereoselectivity for the *exo* or *endo* diastereoisomers. For example, the reaction of cyclopentadiene with (*E*)-cinnamaldehyde (entry 2) showed only a small preference for the *exo* diastereoisomer (*exo*:*endo* 57:43), but gave the *exo* product in 93 % ee. The reaction of acrylaldehdye and crotonaldehyde with a small range of dienes was also described. Interestingly, the addition of 5 % water (by volume) was found to increase both reaction rate and enantioselectivity.[22] Later investigations into this effect by Tomkinson and co-workers found the addition of water increased the concentration of free aldehyde over its dimethyl acetal, increasing reaction rate.[35] The rate of catalyst hydrolysis from the products was also increased thereby reducing retro Diels-Alder reactions that led to lower enantioselectivity.



Entry	R	Yield (%)	*exo: endo*	*exo* % ee
1		81	50:50	84
2		99	57:43	93
3		85	50:50	91

Table 1.3: Diels-Alder reaction catalysed by imidazolidinone **36**

In order to achieve high enantioselectivity in this process, both the iminium ion geometry and the face of substrate attack must be controlled. It has been established that the preferred conformation of the reactive iminium ion species is (*E*)-isomer **B** as shown in Figure 1.14.[1,36,37,38] The *gem*-dimethyl substitution forces the iminium ion to adopt a geometry such that steric interactions with these methyl groups are minimised i.e. the (*Z*)-isomer **A** is disfavoured and (*E*)-isomer **B** favoured. The stereodirecting benzyl group then directs substrate approach to the iminium ion. Gas-phase DFT calculations[36] and analysis of the iminium ion in both the solid and solution phase[37] have shown the preferred conformation of the molecule places the benzyl substituent over the imidazolidinone ring, blocking the upper face as drawn. Preferential diene attack *anti* to the stereodirecting group leads to the experimentally observed Diels-Alder adducts ***exo*-(1*S*,2*S*,3*S*,4*R*)-38** and ***endo*-(1*R*,2*S*,3*S*,4*S*)-38**.[39]

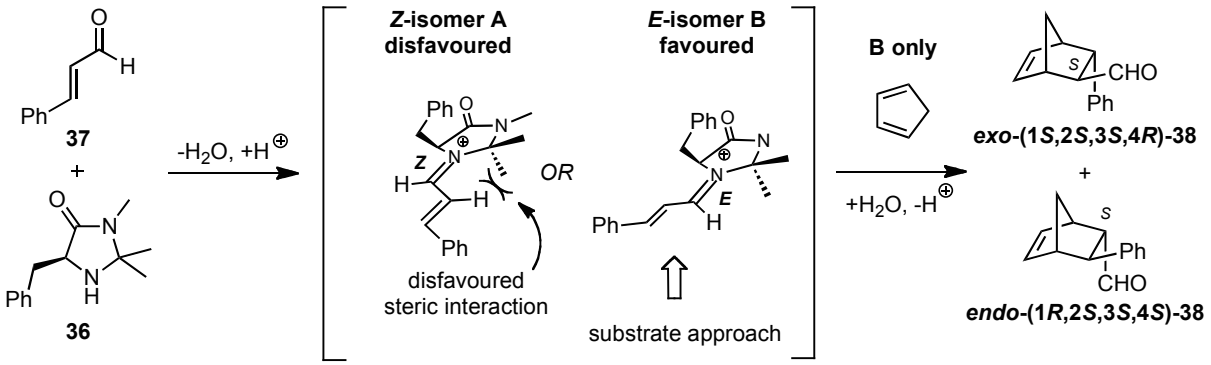
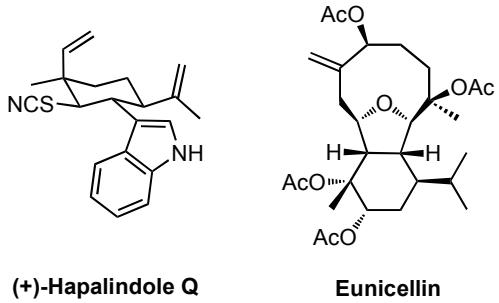


Figure 1.14: Reaction pathway for MacMillan's first generation imidazolidinone **36**

Subsequent work by MacMillan *et al.* showed that imidazolidinone **36** could act as an iminium ion organocatalyst for several other reactions such as nitrone addition[40] and the Friedel-Crafts alkylation of pyrroles.[41] The synthetic utility of this methodology has been shown by its application to the synthesis of natural products such as (+)-Hapalindole Q[42] and Eunicellin (Figure 1.15).[43]

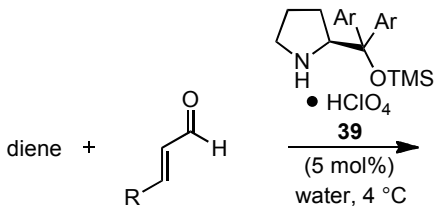


(+)-Hapalindole Q **Eunicellin**

Figure 1.15: Natural products synthesised using imidiazoldinone **36** catalysis

1.2.3.2 Other catalysts

Since the first publications using imidazolidinones as organocatalysts, a number of compounds with markedly different structures have been applied to the iminium-ion promoted Diels-Alder reaction.[44] Catalyst **39** (the perchlorate salt of compound **20**, described in Section 1.1.4) was initially successfully employed in toluene[45] but neat reaction in the presence of water was found to be superior in terms of both rate and enantioselectivity (selected examples in Table 1.4).[46] The cycloaddition of cyclopentadiene and a range of α,β-unsaturated aldehydes proceeded with excellent enantioselectivity and high *exo* diastereoselectivity (97 % *exo* ee, 80:20 *exo*:*endo* with cinnamaldehyde, entry 1). Selected reactions of an aldoester and acrolein with different dienes were also reported (entries 2 and 3). Jørgensen *et al.*[47] and others[44] have extended the scope of similar diarylprolinol silyl ether catalysts to hetero-Diels-Alder reactions, although these operate *via* enamine intermediates.



Entry	Diene	R	Product	Yield (%)	% ee
1[a]		Ph	CHO, Ph (*exo*:*endo* 80:20)	93 (*exo: endo*) (80:20)	84 (*exo*)
2		CO_2Et	CHO, CO_2Et	89	93
3[b]		H	CHO	72	91

Table 1.4: *exo*-Selective Diels-Alder reaction catalysed by **39** (Ar = 3,5-$(CF_3)_2$-C_6H_4)
a) Reaction at RT; b) 10 mol% catalyst used

A five-membered ring is not a prerequisite for catalytic activity, however, as exemplified by acyclic catalyst **40** (Figure 1.16).[48] Maruoka *et al.* showed that a binaphthyl amine could be used to perform an iminium catalysed reaction with high enantioselectivity and excellent *exo* diastereoselectivity (93:7 *exo*:*endo* for the reaction of (*E*)-cinnamaldehyde **37** and cyclopentadiene). The main limitations of this methodology were the need for extended reaction times and a lack of reactivity with dienes other than cyclopentadiene (both cyclohexadiene and 1,3-pentadiene gave only traces of cycloadduct product).

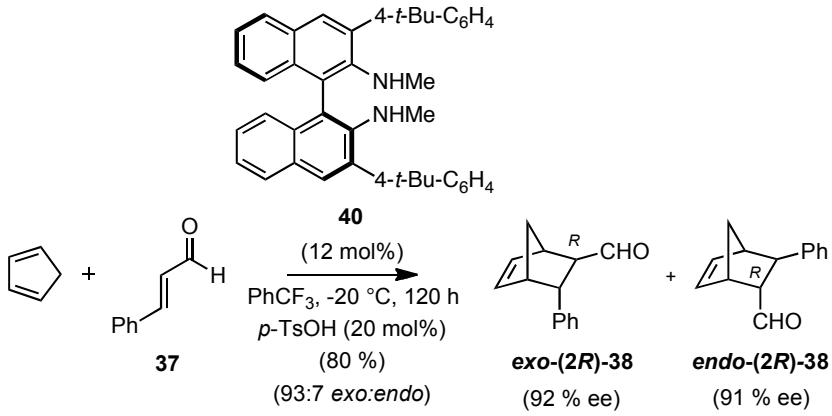


Figure 1.16: *exo*-Selective Diels-Alder reaction catalysed by **40**

Recently, the first examples of enantioselective cycloadditions catalysed by primary amines have been reported.[49] Catalyst **42**, derived from phenylalanine, was developed specifically for challenging α-acyloxyacroleins, such as **41** (Figure 1.17).[50] Such aldehydes are inactive with MacMillan's secondary amine imidazolidinone catalysts.[51]

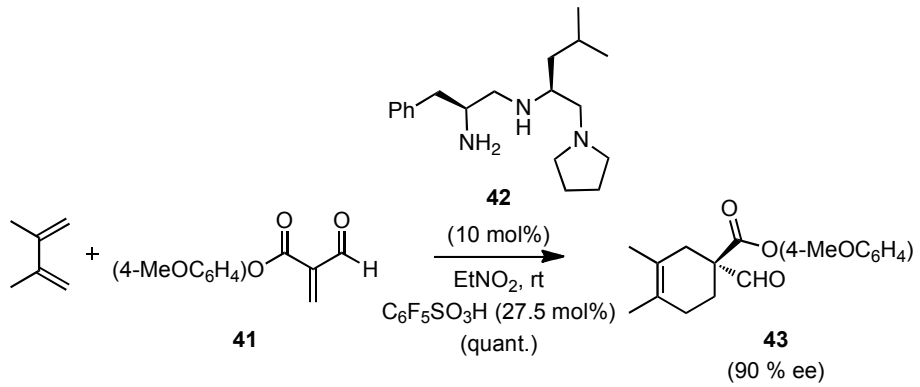


Figure 1.17: Diels-Alder reaction catalysed by primary amine **42**

The observed enantioselectivity in this process was attributed to the creation of a pseudo 5-membered transition state by hydrogen bonding of the iminium ion to other amine groups in the catalyst (Figure 1.18). This *in situ* ordering of the catalyst structure helps to favour the (*Z*)-iminium geometry, with the diene substrate approaching from the opposite face to the adjacent benzyl stereodirecting group.

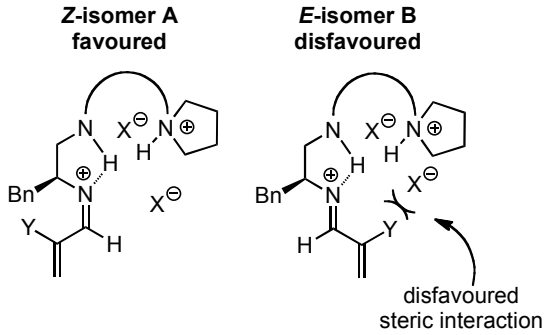


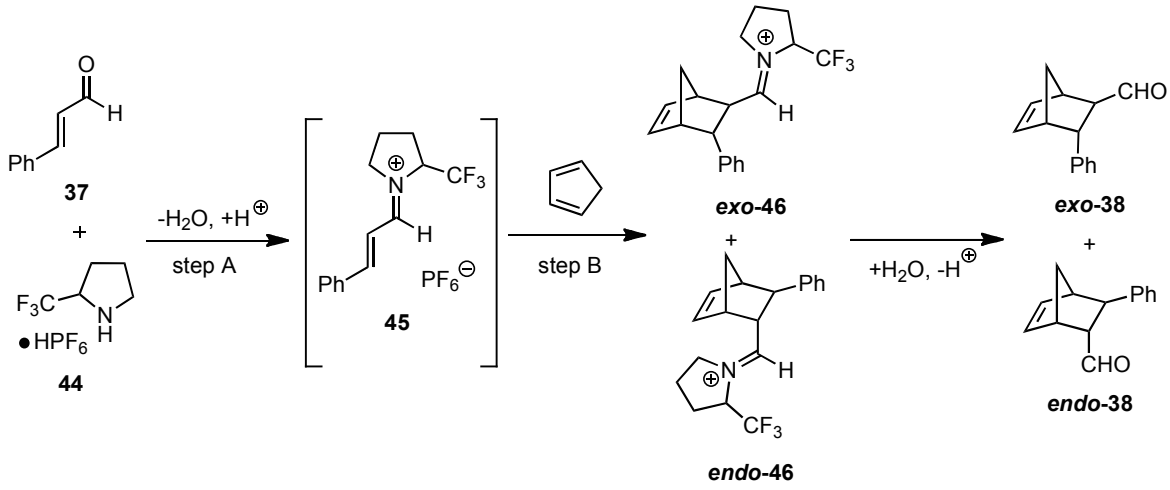
Figure 1.18: Origin of stereoselectivity with catalyst **42**

1.2.3.3 Mechanistic studies

Although great strides have been made in the development of new catalysts, the field of iminium ion organocatalysis is still at an early stage in terms of understanding the mechanistic intricacies of different catalysts. This has begun to be addressed by the use of computer modelling and isolation of reactive intermediates.[36,37] It was originally postulated by MacMillan *et al.* that both the iminium ion formation step and the carbon-carbon bond forming step influence the overall rate of reaction with imidazolidinone catalyst **36** (Section 1.2.3.1).[1] However, a kinetic study of the iminium ion catalysed Diels-Alder reaction of (*E*)-cinnamaldehyde **37** and cyclopentadiene was later reported by Tomkinson and co-workers.[52] Trifluoromethyl pyrrolidine **44** was identified as an effective catalyst (10 mol%, 93 % conv. after 6 h, *exo*:*endo* 68:32) which allowed the reaction to be followed by a

combination of ^{1}H and ^{19}F NMR spectroscopy The hexafluorophosphate salt of pyrrolidine **44** provided an isolatable (*E*)-iminium ion intermediate **45** that could be analysed by X-ray crystallography and allowed the rates of both iminium ion formation and the cycloaddition step to be studied independently (Figure 1.19).

The study showed that, for this reaction, the rate-determining step was the cycloaddition step which was approximately six times slower than iminium ion formation. It was found that the key factor was the Arrhenius parameter *A*, which is ten orders of magnitude smaller for step B, and this was attributed to the stricter steric requirements necessary for cycloaddition over iminium ion formation. In addition, the presence of the electron withdrawing trifluoromethyl moiety adjacent to the reactive centre served to lower the LUMO energy of the iminium ion intermediate, leading to acceleration of the kinetically significant cycloaddition step.



Reaction Step	k_{293} ($x10^{-3}$ dm^3 mol^{-1})	E_a /kJ mol^{-1}	*A* /s^{-1}
A	2.65	100	5.89×10^{14}
B	0.374	45.1	4.14×10^{4}

Figure 1.19: Kinetic parameters for Diels-Alder reaction catalysed by pyrrolidine **44**

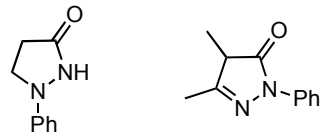
The Diels-Alder cycloaddition remains one of the most powerful methods for the synthesis of complex ring structures. As a result of its synthetic utility, it is unsurprising that the Diels-Alder reaction has become something of a benchmark transformation by which to evaluate new asymmetric organic catalysts.[22] The potential for iminium ion organocatalysts with a range of structures to effectively accelerate reactions and control stereoselectivity is also now well established.

1.3 Pyrazolidin-3-ones

This report focuses on the pyrazolidin-3-one framework and its use as both a catalyst and a substrate in organocatalysed reactions. The following section outlines selected recent applications of pyrazolidinones as reaction substrates.

1.3.1 Pyrazolidin-3-ones as substrates

Pyrazolidin-3-ones are 5-membered ring heterocycles containing two adjacent nitrogen atoms and a carbonyl at the three position. Two examples of commercially used pyrazolidin-3-ones are Phenidone, used as a photographic developer, and Edaravone which is sold as a neuroprotective agent (Figure 1.20).[53]



Phenidone **Edaravone**

Figure 1.20: Commercially used pyrazolidino-3-ones Phenidone and Edaravone

Azomethine imines are 1,3-dipolar compounds readily derived from pyrazolidin-3-ones by condensation with an aldehyde.[54] They have recently found substantial application in catalysed [3+2] cycloadditions with a range of suitable partners.[55] A recently reported example also showed their potential utility as electrophiles, in this case under attack by trimethyl(trifluoromethyl)silane (Figure 1.21).[56] Reaction proceeds under phase transfer conditions, using chiral alkaloid catalyst **50**. The subsequent products can be readily converted to valuable trifluoromethylated amines, such as **49**, by treatment with Raney nickel and acid.

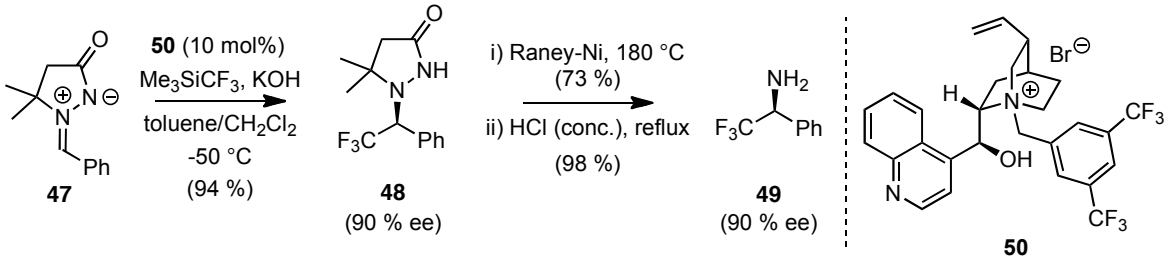


Figure 1.21: Phase transfer catalysis using **50** and conversion of products to trifluoromethylated amine **49**

Sibi and co-workers have reported the use of pyrazolidinone crotonate dipolarophiles in enantioselective Lewis acid catalysed Diels-Alder reactions (Figure 1.22).[57] The pyrazolidinone acts as a template for the active copper/ligand complex and this leads to a locking in the configuration of the previously configurationally labile N(1)-benzyl substrate.

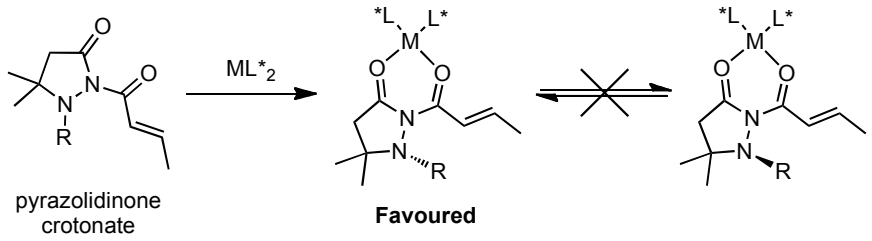
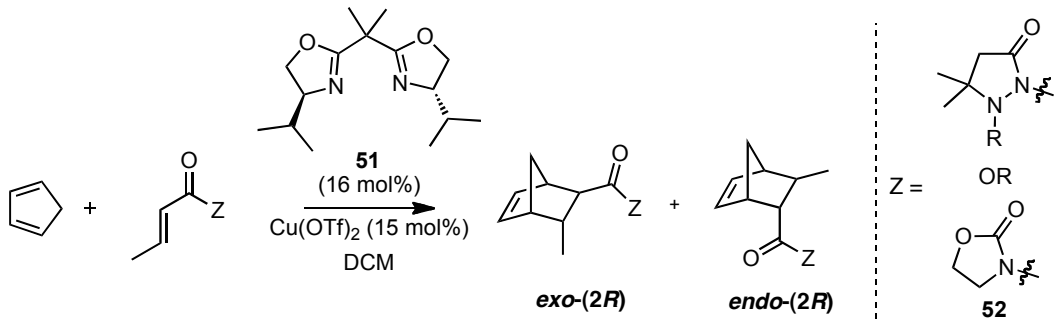


Figure 1.22: Chiral relay from chiral ligands to N(1) pyrazolidinone substituent

This newly created stereocentre then acts in concert with the chiral ligands to direct the approach of a diene to the dienophile. Catalysis results for a series of templates with copper triflate and bisoxazoline **51** are outlined in Table 1.5. For oxazolidinone **52** (entry 1) and an *N*(1)-unsubstituted pyrazolidinone (entry 2), enantioselectivity is poor due to the absence of chiral relay. However, enantioselectivity improves markedly when an *N*(1)-benzyl substituent is employed (entry 3) and increases with increasing steric bulk in the chiral relay group (entry 4). The same principle has subsequently been applied to cycloadditions of pyrazolidinone crotonates with nitrones, nitrile oxides and conjugate additions with hydroxylamines and radicals.[58]



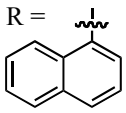
Entry	Z	*exo*:*endo*	*endo* % ee
1	**52**	13:87	23
2	R = H	5:95	8
3	R = 	7:93	71
4	R = 	10:90	92

Table 1.5: Diels-Alder cycloaddition using pyrazolidinone templates

The same research group were then able to modify this methodology to obtain enantioenriched pyrazolidinones by kinetic resolution (Figure 1.23). The copper/bisoxazoline **54** complex showed excellent selectively for the (*R*)-enantiomer of pyrazolidinone crotonate **53** which underwent Diels-Alder reaction thereby leaving **(*S*)-55** with 98 % ee, eventually isolated in

40 % yield. The Diels-Alder adduct ***endo*-(2R)-56** could be cleaved with lithium *p*-methoxybenzyloxide to access the (*R*)-enantiomer in 70 % ee.[59]

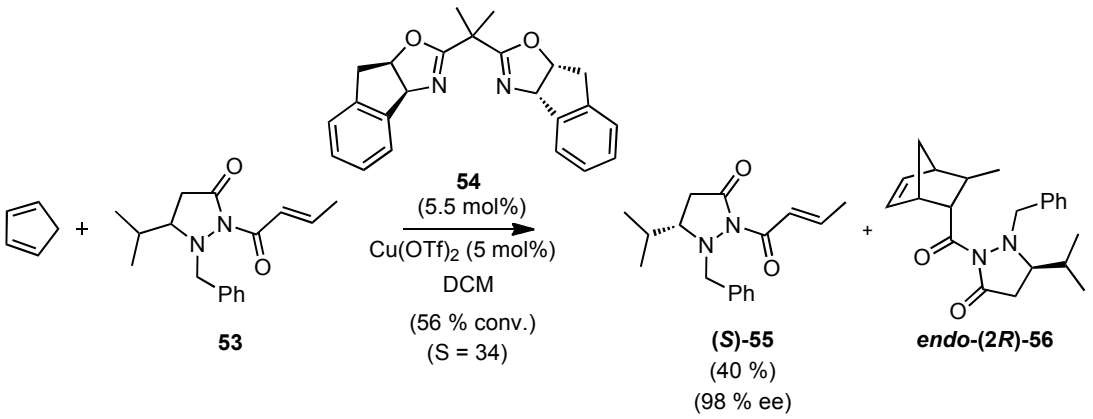
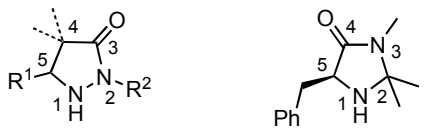


Figure 1.23: Kinetic resolution of **53**

1.3.2 Pyrazolidin-3-ones as potential iminium ion organocatalysts

While extensive progress has been made in the development of highly stereoselective iminium-ion promoted reactions, there is significant potential for improvement in many areas, notably in reaction diastereoselectivity, lowering catalyst loading and reducing reaction time. In addition, new catalysts may help to improve our understanding of iminium ion reaction mechanisms. Hence, there remains a need for the development of new selective and efficient organocatalytic methods, in order to build on those already established.

This report focuses on the pyrazolidin-3-one framework (Figure 1.24) as this possesses the potential to act as an effective iminium ion organocatalyst. It shares a number of similarities to MacMillan's imidazolidinone catalyst **36**, also shown in Figure 1.24; both frameworks possess a nitrogen atom with a lone pair capable of acting as a nucleophile, essential for formation of the reactive iminium ion. In both cases, this nitrogen is held within a constrained five-membered ring that can be adorned with stereodirecting groups. While imidazolidinone **36** contains a *gem*-dimethyl moiety at the C(2) position, this structural motif could be included in the pyrazolidinone backbone at C(4), fixing the orientation of any adjacent stereodirecting groups present.[60] Furthermore, the introduction of this *gem*-dimethyl group blocks any possible enolisation at the C(4) position of the catalyst.



Pyrazolidin-3-one **Imidazolidinone 36**

Figure 1.24: Pyrazolidin-3-one framework and imidazolidinone **36**

Despite their structural similarity, the pyrazolidinone scaffold contains several features that differentiate it from imidazolidinone **36** and may potentially lead to enhanced rate acceleration and possibly high levels of enantioselectivity in catalysis. There are two sites available for substitution, namely at N(2) and C(5). It was envisaged that C(5) substitution would primarily be useful for introducing a stereodirecting group. Such a group could control the face of attack on an iminium ion intermediate, in analogy to the benzyl group at C(5) of imidazolidinone **36**. However, the N(2) position, adjacent to the nucleophilic centre, may also be derivatised. It is anticipated that substitution here would give a defined transoid (*E*)-iminium geometry by disfavouring the (*Z*)-iminium (**A** and **B** in Figure 1.25). The nature of the substituent could also be used to control the steric and electronic environment of the adjacent nucleophilic centre. Using these principles, it should be possible to fine tune catalytic properties by variation of the substituents, allowing scope for the development of a highly efficient and stereoselective organocatalyst. Also possible are the two cisoid iminium conformations **C** and **D** however these are likely to be sterically disfavoured compared to the transoid conformations (related catalysts have been found to be exclusively in the transoid conformation).[37,52]

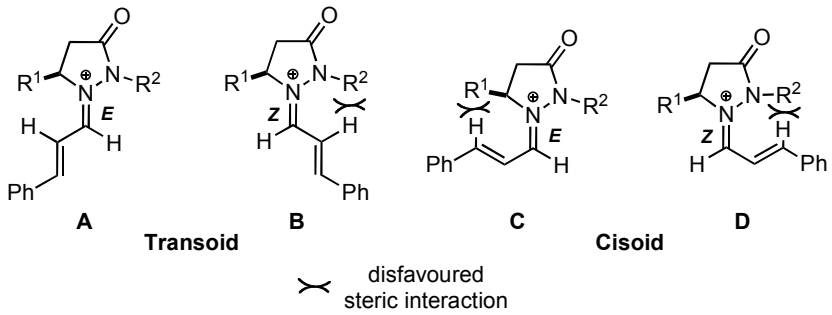


Figure 1.25: Proposed pyrazolidinone derived iminium ions

At the outset of research, the rate-determining step for iminium ion Diels-Alder cycloadditions had not been established. MacMillan had postulated that both iminium ion formation and the cycloaddition step were important.[22] Hence, a further feature of the pyrazolidinone framework, which made it attractive as an organocatalyst was the potential for increasing catalyst nucleophilicity by the α-effect. This may result in accelerated iminium formation and potentially an increase in reaction rate. The source of this effect is outlined in the next section.

1.3.2.1 The α-effect

Nucleophiles such as HOO^-, $HONH_2$ and N_2H_4 that contain a heteroatom possessing a lone pair of electrons adjacent to their nucleophilic site are often considered as exceptional nucleophiles.[61] The presence of this adjacent lone pair leads to an increase in the rate of

nucleophilic attack on electrophiles, in comparison to related structures containing no such lone pair. One plausible rationalisation for this effect uses frontier molecular orbital theory. It states that overlap of the orbital containing the electrons on the nucleophilic atom and the lone pair on the adjacent heteroatom will cause a splitting in energy levels of the molecular orbitals of the molecule.[61] This leads to the HOMO being raised in energy, relative to the unsubstituted nucleophile, and, therefore, the nucleophilicity increases. A schematic example of this analysis using the peroxide anion is shown in Figure 1.26.

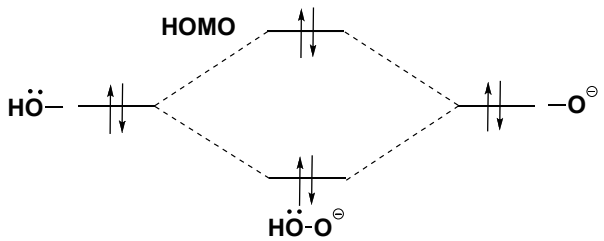
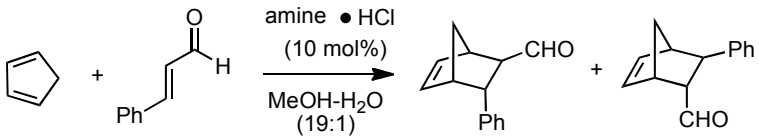


Figure 1.26: α-Effect on the HOMO of the peroxide anion

Increasing catalyst nucleophilicity was a strategy employed by MacMillan in order to increase the rate of iminium ion formation with his second generation imidazolidinone catalysts.[62] Hence, it would be anticipated that the presence of the α-effect would be beneficial to iminium ion formation with a structurally related pyrazolidinone catalyst. For the pyrazolidinone framework, the presence of the lone pair on the N(2) atom could potentially give rise to increased nucleophilicity at N(1) and so increase the rate of iminium ion formation.

1.3.2.2 Related catalyst architectures

The reactivity of hydrazides as organocatalysts was elegantly presented in a series of papers by Tomkinson and co-workers.[63,64,65] They examined the cycloaddition of (*E*)-cinnamaldehyde **37** and cyclopentadiene, catalysed by a series of cyclic and acylic hydrazides (Table 1.6). Dimethylamine gave only a 22 % yield after 48 h (entry 1). Introduction of an adjacent nitrogen in *N*,*N*'-dimethylhydrazine led to a rate acceleration and this was attributed to enhanced catalyst nucleophilicity due to the α-effect (entry 2). Interestingly, the introduction of a β-electron withdrawing group was found to give a significant further rate acceleration (entry 3). Incorporation of this hydrazide ester group into a 5-membered ring led to a large drop in reactivity (entry 4) but expansion to a six-membered ring gave a catalyst with 90 % conversion in just 3 h (entry 5). Calculations on a selection of these compounds indicated a correlation of reactivity with the E_{LUMO} value of the respective iminium ions, consistent with cycloaddition being the rate-determining step.[52,66]



37 ***exo*-38** ***endo*-38**

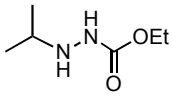
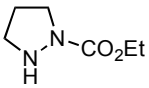
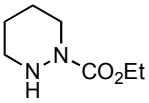
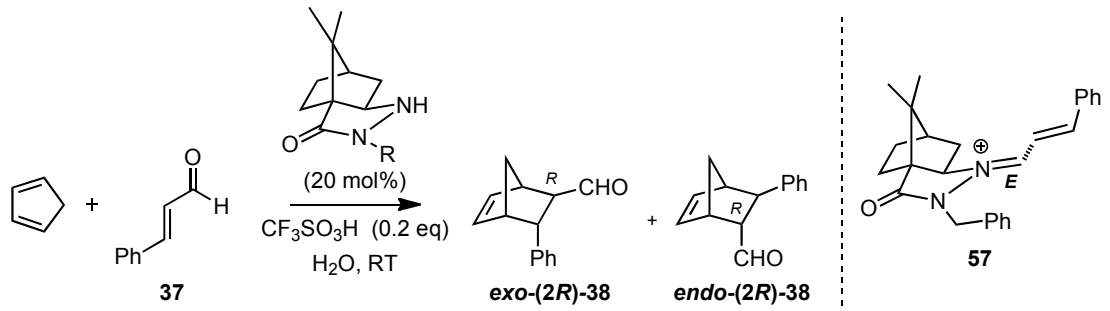
Entry	Structure	Time (h)	Yield (%)	*exo: endo*
1[a]		48	22	62:38
2[a]		72	48	32:68
3		6	90	66:37
4		24	38	67:33
5		3	90	68:32

Table 1.6: Diels-Alder reaction catalysed by acyclic amines
a) 5 mol% water added

An asymmetric pyrazolidinone catalyst derived from camphorsulfonic acid was described by Ogilvie and co-workers (entry 1, Table 1.7).[67] Optimal catalyst performance was observed in water alone, giving Diels-Alder adducts ***exo*-(2*R*)-38** and ***endo*-(2*R*)-38** in 96 % yield and an *exo*:*endo* ratio of 65:35. ***exo*-(2*R*)-38** was produced with 90 % ee. A combination of ^{1}H NMR spectroscopic analysis and theoretical calculations on the key iminium intermediate **57** led to the introduction of an (*R*)-α-methylbenzyl N-protecting group which gave improved diastereo- and enantioselectivity (entry 2).[68] The introduction of a second stereocentre was designed to increase conformational control by disfavouring a (*Z*)-geometry in the C=N bond of the key iminium ion intermediate **57** (the favoured (*E*)-geometry is displayed in the figure). Use of the alternative (*S*)-α-methylbenzyl N-protecting group led to a decrease in enantioselectivity (entry 3). A related system derived from (+)-pugelone was recently described by Bach.[69]



Entry	R	Yield (%)	*exo: endo*	*exo* % ee
1		96	65:35	90
2		94	74:26	95
3		55	65:35	74

Table 1.7: Asymmetric Diels-Alder reaction catalysed by chiral pyrazolidinone

Lee and co-workers initially reported a structurally related sulfonyl hydrazide, also derived from camphor sulfonic acid, for the same reaction.[70] However, reaction with ketones was found to be limited so a second-generation catalyst **59** was designed incorporating a primary, rather than secondary, hydrazine (Figure 1.27).[71] **59** showed much improved reactivity with a range of ketones, such as **58**.

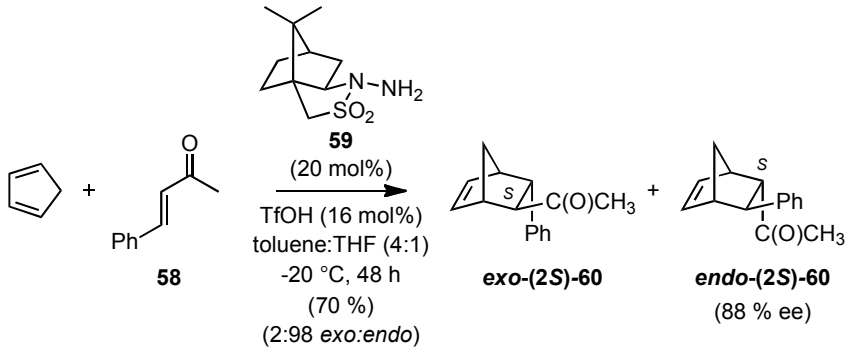


Figure 1.27: Asymmetric Diels-Alder reaction catalysed by chiral sulfonyl hydrazide

The first example of a chiral acyclic hydrazide catalyst was recently reported (Figure 1.28).[72] Di-hydrazide **61** was found to catalyse Diels-Alder reactions with good enantioselectivity, though, in the majority of cases, little diastereoselectivity.

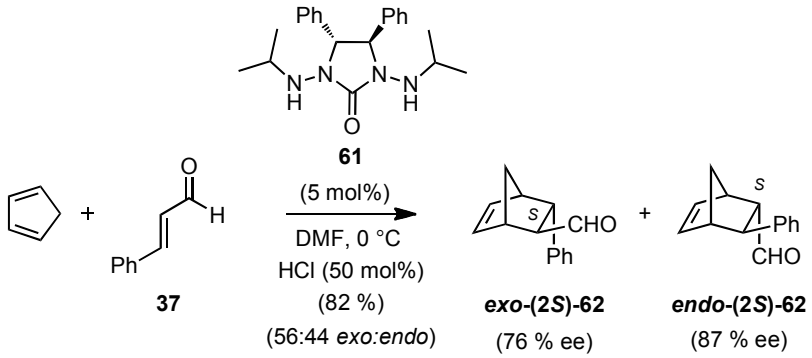
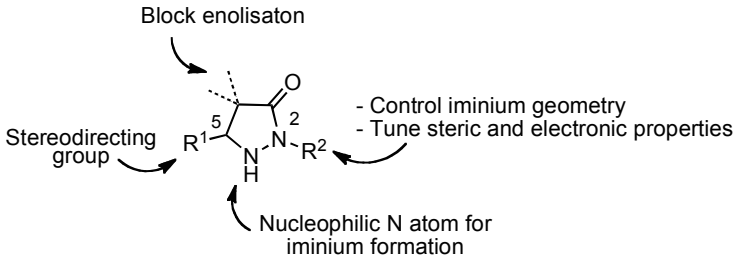


Figure 1.28: Diels-Alder reaction catalysed by hydrazide **61**

1.4 Aims and objectives

The pyrazolidin-3-one framework contains a number of structural features that suggest it will be an effective source of iminium ion organocatalysts.



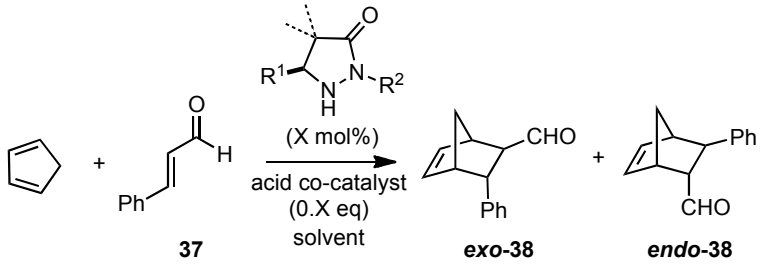
Initial aims were to:

i) Develop a robust synthetic route to racemic series of pyrazolidinones capable of introducing a variety of potential substituents at C(5) and N(2).

ii) Find suitable conditions and test these compounds as catalysts of the Diels-Alder cycloaddition.

iii) Use this information to design a highly reactive, diastereo- and enantioselective asymmetric pyrazolidinone catalyst.

iv) Investigate the mechanism of action to gain insight into iminium catalysed processes.



Chapter 2: Racemic iminium ion organocatalysis

This chapter details the establishment of a synthetic route to access a small range of potential organocatalysts based upon the pyrazolidin-3-one template, utilising and elaborating on a route previously developed within the group.[73] A series of *N*(2)-benzyl substituted pyrazolidinones were targeted with either methyl, phenyl, *iso*-propyl or trifluoromethyl substitution at the C(5) position (Figure 2.1). A series of *C*(5)-methyl substituted pyrazolidinones were also targeted with varying N(2) substituents bearing both alkyl and electron-withdrawing groups. In addition, methods for the introduction of a *gem*-dimethyl group at C(4) were evaluated and the synthesis of a pyrazolidinone with *gem*-dimethyl substitution at C(4) described. These catalysts were then tested for activity in the Diels-Alder cycloaddition of (*E*)-cinnamaldehyde and cyclopentadiene with particular focus on substitution patterns that led to enhanced reaction rate. These results led to the design of catalysts **114** and **115** which had $t^{1/2}$ values of approximately 1 h. The substrate scope of the **114** catalysed reaction was also delineated.

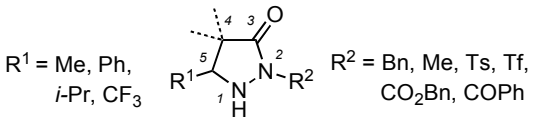


Figure 2.1: Pyrazolidinones targeted as potential organocatalysts

2.1 Prior work undertaken in Smith group

This section describes limited previous research carried out within the Smith group by Scott Phillips concerned with the design of a simple synthetic route to differentially protected pyrazolidin-3-ones, with particular reference to the introduction of substitution at both C(5) and N(2). Such a route should allow rapid access to a range of such compounds for testing as potential iminium ion organocatalysts.

The initial synthetic pathway investigated toward this scaffold is shown retrosynthetically in Figure 2.2. A pyrazolinone could be synthesised from the condensation of mono-substituted hydrazines with an appropriate β-keto-ester, followed by cyclisation. Reduction of the imine functionality would then give the desired pyrazolidinones.

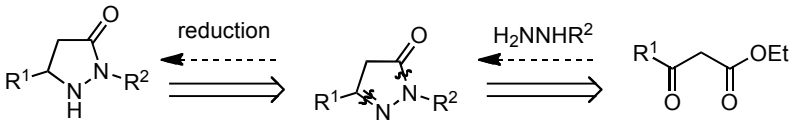
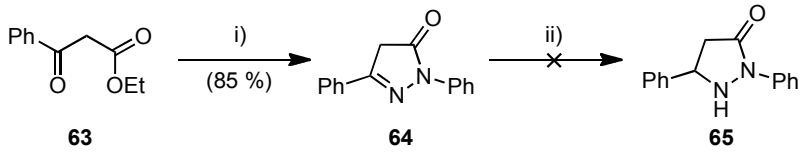


Figure 2.2: Initial retrosynthesis of pyrazolidinone scaffold

Pyrazolinone **64** was readily accessed from β-keto-ester **63** however the product proved completely resistant to both standard reducing agents (i.e. $NaBH_4$, $LiAlH_4$, hydrogenation) and others previously effective for structurally analogous substrates such as Superhydride ($LiBEt_3H$) and sodium cyanoborohydride (Scheme 2.1).[67,74]



63 **64** **65**

Scheme 2.1: *Reagents and conditions*: i) phenylhydrazine, EtOH, reflux; ii) $NaBH_4$, EtOH, rt, or $LiAlH_4$, THF, 0 ºC, or $LiBEt_3H$, CH_2Cl_2, -78 ºC to rt, or $NaCNBH_3$, acetic acid-MeOH (2:1), rt.

An alternative route to the desired pyrazolidinone scaffold was envisaged utilising the conjugate addition of hydrazines to α,β-unsaturated esters (Figure 2.3). Such compounds could potentially be accessed in just a single step from an α,β-unsaturated ester and a mono-substituted hydrazine (route A). Alternatively, hydrazine itself would give a mono-substituted pyrazolidinone (route B). The increased nucleophilicity of the N(1) position of a pyrazolidinone over the N(2) position could then be exploited to selectively introduce a protecting group at N(1), followed by selective N(2) functionalisation and protecting group removal.

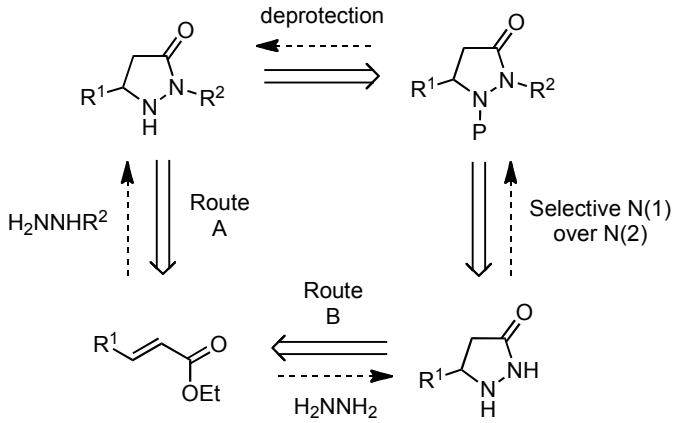
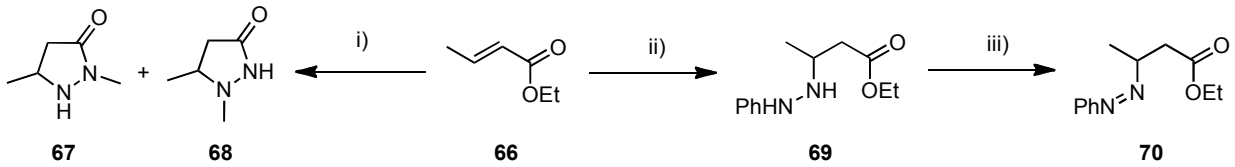


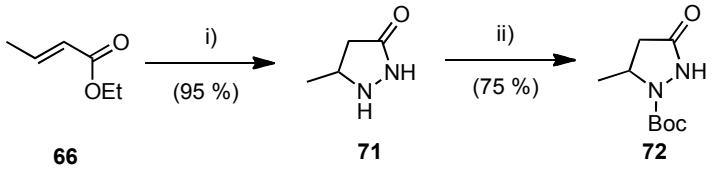
Figure 2.3: Alternative retrosynthesis of pyrazolidinone scaffold

The successful use of mono-substituted hydrazines would allow the most rapid access to the desired pyrazolidinone motif and this route was examined first. The reaction of ethyl crotonate **66** with methylhydrazine gave a 50:50 mixture of pyrazolidinones **67** and **68**, indicating an insufficient difference in nucleophilicity between the two nitrogens of methylhydrazine for effective regiocontrol (Scheme 2.2). When phenylhydrazine was used instead, only the uncyclised intermediate **69** could be isolated. Attempts to promote cyclisation of **69** by refluxing in toluene were unsuccessful, yielding only the oxidation product **70**.



Scheme 2.2: *Reagents and conditions*: i) methylhydrazine, MeOH, reflux; ii) phenylhydrazine, MeOH, reflux; iii) toluene, reflux.

Due to the issues of regioselectivity and the formation of undesired oxidation products, this route was not investigated further. Instead, attention turned to using hydrazine itself to access the desired pyrazolidinone architecture (Scheme 2.3). Formation of the pyrazolidinone ring by the conjugate addition/cyclisation of ethyl crotonate **66** with hydrazine hydrate, following the method of White *et al.* proceeded smoothly[75] and subsequent *N*(1)-Boc protection took place selectively at N(1), as desired, to give compound **72** (Scheme 2.3).[76]



Scheme 2.3: *Reagents and conditions*: i) hydrazine hydrate, EtOH, reflux; ii) di-*tert*-butyl dicarbonate, Na_2CO_3, dioxane-H_2O, rt.

From **72**, it was hoped to selectively introduce functionalisation at N(2) through reaction with an appropriate electrophile (Figure 2.4). However, the pyrazolidinone framework contains two potential nucleophilic centres. In addition to the N(2) position, reaction at the oxygen on C(3) would also be possible, giving rise to undesired side-products. (This regioselectivity issue will be further explored in Section 2.3.1).

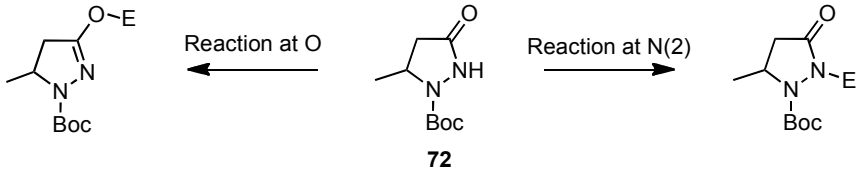
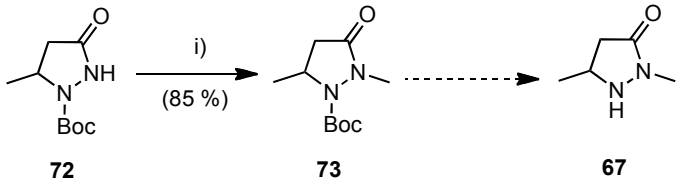


Figure 2.4: Potential products of attempted N(2) derivatisation (E = electrophile)

Pleasingly, treatment of **72** with potassium carbonate, followed by iodomethane, showed exclusively *N*(2)-methylation to give the known compound **73** in 85 % yield (Scheme 2.4),[76] although the final step, *N*-Boc deprotection to give the desired amine **67**, was not attempted.



Scheme 2.4: *Reagents and conditions*: i) CH_3I, DMF, K_2CO_3, rt.

In summary, at the outset of experimental work a number of methods towards the synthesis of N(2) substituted pyrazolidinones had previously been evaluated within the Smith group. The successful route utilised hydrazine itself in the conjugate addition/cyclisation reaction with ethyl crotonate to give the pyrazolidinone framework, which could be elaborated to selectively introduce substitution at N(1) and N(2). However, the application of this route to the desired catalysts was not fully delineated.

2.2 Synthesis of *N*(2)-benzyl substituted pyrazolidinones

2.2.1 Completion of synthetic protocol development

On commencement of the project, the first task was to finish evaluation of the synthetic route partially explored in-house and so establish a reliable route to the desired pyrazolidinones. The initial target was *C*(5)-methyl, *N*(2)-benzyl compound **76** (Scheme 2.5). By this route, **76** would be accessed from previously synthesised *N*(1)-Boc protected compound **72** and so the synthesis of **72** was successfully repeated in order to obtain more material. It had previously been established that compound **72** could be readily methylated at N(2) and it was found that analogous reaction conditions could also be employed to introduce a benzyl protecting group at N(2), leading to compound **74**. This route proved amenable to large scale synthesis, with 19.3 g (21.0 ml) of ethyl crotonate **66** yielding 19.9 g of intermediate compound **74** in 3 steps with 41 % overall yield. A crystal structure obtained of compound **74** confirmed direct *N*-benzylation had been achieved (Figure 2.5).

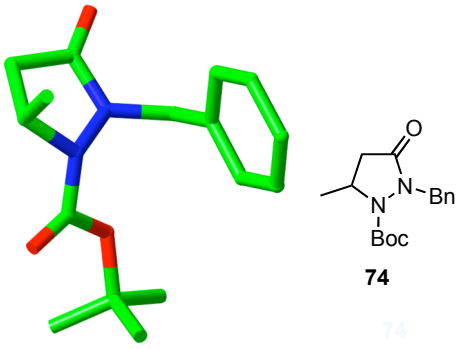
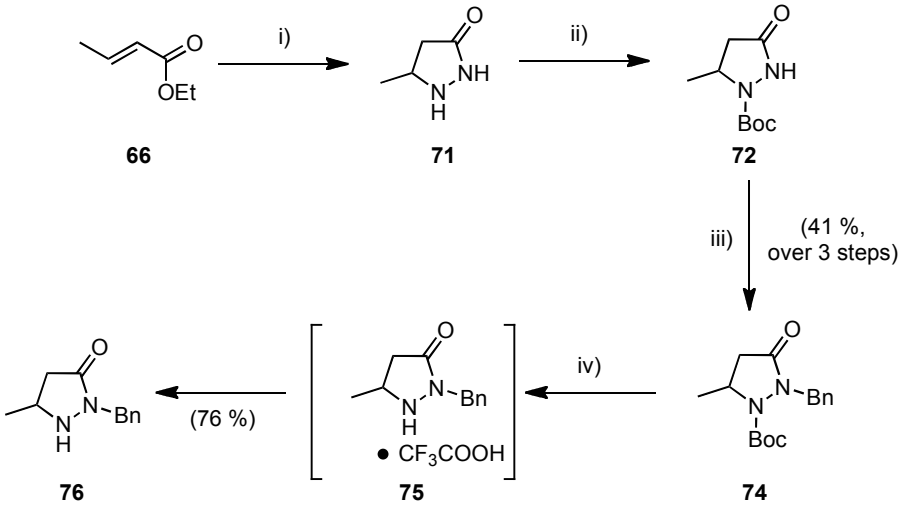


Figure 2.5: Molecular representation of the single crystal structure of **74**

N-Boc-deprotection with trifluoroacetic acid proceeded smoothly but gave amine salt **75** as a thick oil containing significant amounts of residual acid, which could not be readily removed under high vacuum (similar issues were also encountered when tetrafluoroboric acid was used). To overcome this, **75** was treated with triethylamine to generate the free amine **76** and

neutralise the excess acid. This gave the desired *C*(5)-methyl substituted pyrazolidinone **76** which could be taken on for testing in catalysis.

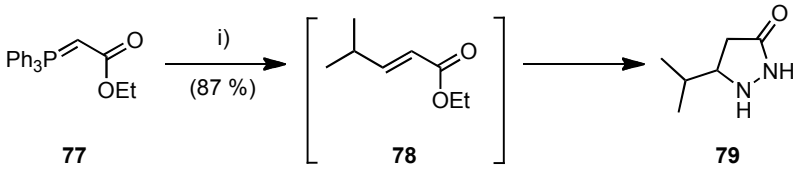


Scheme 2.5: *Reagents and conditions*: i) hydrazine hydrate, EtOH, reflux; ii) di-*tert*-butyl dicarbonate, Na_2CO_3, dioxane-H_2O, rt; iii) benzyl bromide, DMF, K_2CO_3, rt; iv) TFA, CH_2Cl_2, rt, then NEt_3, CH_2Cl_2, rt.

2.2.2 Expansion to other *N*(2)-benzyl derivatives

With a synthetic route established, further investigation targeted the synthesis of *N*(2)-benzyl pyrazolidinones bearing a phenyl, *iso*-propyl and trifluoromethyl substituent at C(5). Each of these compounds could be readily accessed from the appropriate α,β-unsaturated ester by making use of the general synthetic route established in the synthesis of **76**. This would then allow the effect of the C(5) group on catalysis to be examined independently of other substitution on the ring.

The only required α,β-unsaturated ester not commercially available was *iso*-propyl ester **78** (Scheme 2.6) but this was readily accessible from a stereoselective Wittig reaction of *iso*-butyraldehdye and phosphorane **77** ((*E*):(*Z*) ratio of >20:1 as judged by ^{1}H NMR spectroscopic analysis of the crude product residue).[77] Due to the relatively high volatility of **78**, the crude material was not fully isolated but was partially purified by passing through a silica plug, to remove residual triphenylphosphine oxide, and then directly treated with hydrazine hydrate to give pyrazolidinone **79** in 87 % overall yield.



Scheme 2.6: *Reagents and conditions*: i) *iso*-butyraldehdye, CH_2Cl_2, 0 ºC to rt, then hydrazine hydrate, EtOH, reflux.

With the necessary starting materials in hand, α,β-unsaturated esters **78**, **81** and **82** were derivatised using the chemistry developed with *C*(5)-methyl catalyst **76** (Scheme 2.7). Reflux with hydrazine hydrate in ethanol proceeded smoothly with trifluoromethyl ester **82** but reaction with ethyl cinnamate **81** produced a mixture of ester **81**, pyrazolidinone **83** and a significant quantity of a structurally related by-product **80** in the ratio 11:56:33 (**81:83:80**). The structure of by-product **80** has not been unambiguously determined but was hypothesised from the ^{1}H NMR spectrum to correspond to one of the two structures shown in Figure 2.6, which would result from either mono (**80a**) or di-addition (**80b**) of hydrazine to ethyl cinnamate **81**. A second reflux in toluene resulted in full conversion of intermediate **80** to pyrazolidinone **83** with the structure of **83** confirmed by mass spectrometry and X-ray crystallography (Figure 2.7).

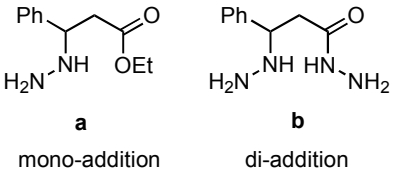


Figure 2.6: Potential structures of by-product **80**

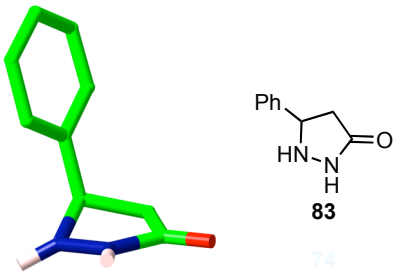
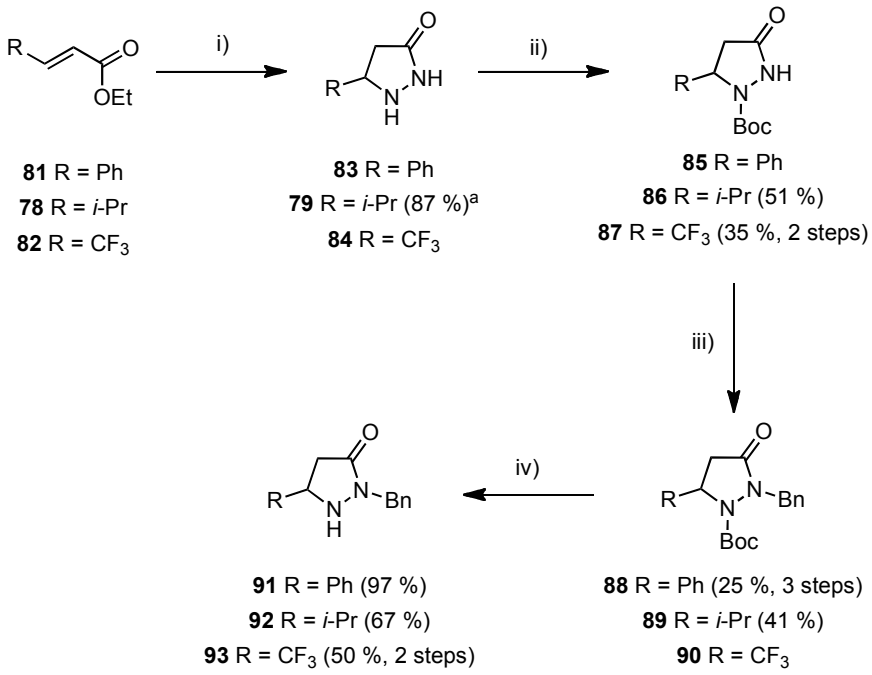


Figure 2.7: Molecular representation of single crystal structure of 5-phenylpyrazolidin-3-one **83**

N(1)-Boc protection with all pyrazolidinones proceeded smoothly, though *C*(5)-trifluoromethyl compound **87** required a modified work-up due to its unusually high water solubility. Selective *N*(2)-benzylation of compounds **85-87** was in all cases straightforward and subsequent *N*(1)-Boc deprotection with trifluoroacetic acid, followed by washing with saturated sodium bicarbonate solution liberated the free amines **91-93** with good yields. Compounds **91-93** could then be taken on for testing.



Scheme 2.7: *Reagents and conditions*: i) hydrazine hydrate, EtOH, reflux then toluene, reflux (**80** only); ii) di-*tert* butyl dicarbonate, Na_2CO_3, dioxane-H_2O, rt; iii) benzyl bromide, DMF, K_2CO_3, rt; iv) TFA, CH_2Cl_2, rt then saturated $NaHCO_3$ solution, CH_2Cl_2.
a) Yield from phosphorane **77**

The structure of *C*(5)-trifluoromethyl catalyst **93** was confirmed by X-ray crystallographic analysis (Figure 2.8).

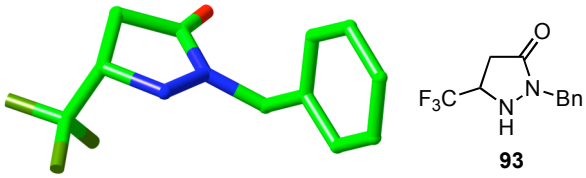


Figure 2.8: Molecular representation of single crystal structure of **93** (the unit cell contains two molecules of **93** but for clarity only one is shown)

2.3 Alternative substitution at N(2)

In addition to exploring the effect of substitution at C(5), it was hoped that catalyst activity could be further optimised by elaboration of the N(2) position. A small range of catalysts were targeted with a common methyl substituent at C(5) and a range of N(2) substitution encompassing *N*-alkyl and electron withdrawing groups (Figure 2.9). This would simplify comparison across the series and allow the effect of N(2) substitution to be evaluated in isolation from other substituent effects.

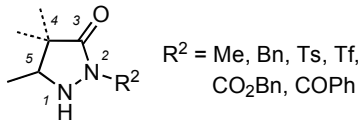
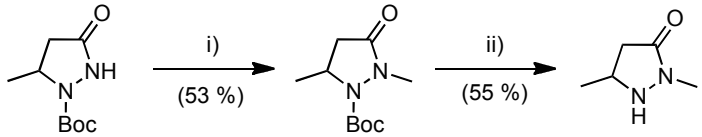


Figure 2.9: Structure of potential N(2) substituted pyrazolidinone catalysts

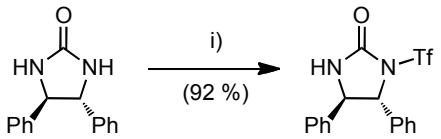
The synthesis of *N*(2)-benzyl substituted catalysts has already been described (see Section 2.2.1) and a method for the introduction of a methyl group at the N(2) position of compound **72** had been partially established in-house, though not fully delineated (see Section 2.1). Compound **72** was treated with potassium carbonate and iodomethane, as before, to give the *N*(2)-methylated compound **73**, albeit in lower yield than previously reported (Scheme 2.8). *N*-Boc-deprotection of the N(1) position, followed by multiple extractions of the aqueous phase with dichloromethane gave a 55 % yield of **67**.



72 **73** **67**

Scheme 2.8: *Reagents and conditions*: i) CH_3I, DMF, K_2CO_3, rt; ii) TFA, CH_2Cl_2, rt, then saturated $NaHCO_3$ solution, CH_2Cl_2.

Similarly to *C*(5)-trifluoromethyl catalyst **93**, we were interested in the effect of electron-withdrawing substituents at the N(2) position. Corey *et al.* had reported that a triflate group could be selectively introduced at nitrogen on structurally related imidazolidin-2-one **94**, despite the potential for *O*-triflation (Scheme 2.9).[78] It was hoped to use this method as a general route for the introduction of electron-withdrawing substituents at the N(2) position, starting with the tosyl functional group.



94 **95**

Scheme 2.9: *Reagents and conditions*: i) NEt_3, CH_2Cl_2, then triflic anhydride, -78 ºC to rt.

Treatment of compound **72** with triethylamine, followed by addition of tosyl chloride led to complete consumption of starting material to give a single product that could be isolated in 46 % yield (Scheme 2.10). However, rather than *N*(2)-tosylation, the product was identified as the *O*-tosylated material **96**. The regioselectivity of the process was proven by ^{15}N NMR (see Section 2.3.1) and by obtaining the crystal structure of **96** (Figure 2.10). Further corroboration came from examination of the ^{1}H NMR spectra where a significant downfield shift of the C(4)H_2 protons of **96** (3.26 and 2.61 ppm) was observed in comparison to those of compound **72** (2.92 and 2.14 ppm). This effect has been observed in analogous systems and is consistent with O functionalisation.[79] A combination of ^{1}H and ^{15}N NMR were used to establish the regioselectivity of further N(2) functionalisation reactions.

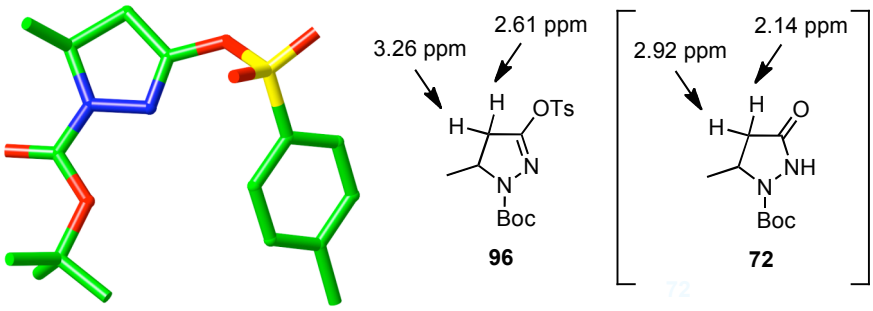
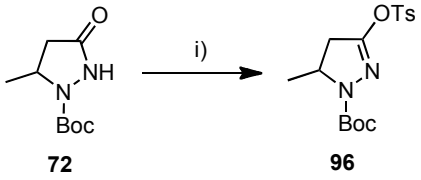


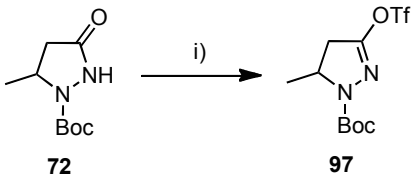
Figure 2.10: Molecular representation of the single crystal structure of *O*-tosyl compound **96** and ^{1}H NMR shifts of the C(4)H_2 protons of **96** and starting material **72**

In an attempt to facilitate N(2) substitution, the base was changed to sodium hydride but, again, full conversion of **72** to exclusively **96** was observed (Scheme 2.10). Potassium carbonate in DMF had previously been shown to selectively introducing alkyl groups at nitrogen (see Sections 2.1). However, in a reaction with tosyl chloride, only the O functionalised compound **96** was again observed in the crude reaction mixture by ^{1}H NMR spectroscopic analysis (Scheme 2.10).



Scheme 2.10: *Reagents and conditions*: i) NEt_3, CH_2Cl_2, then tosyl chloride, -78 ºC to rt (46 %), or NaH, CH_2Cl_2, then tosyl chloride, -78 ºC to rt, or tosyl chloride, DMF, K_2CO_3, rt.

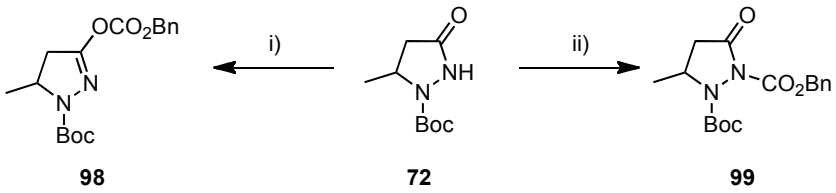
To allow direct comparison of the inherent selectivity of pyrazolidinones in this reaction, the electrophile was changed to triflic anhydride in order to mimic conditions previously employed by Corey (Scheme 2.11). As expected, using triethylamine as base in this reaction resulted in complete conversion of starting material to the *O*-triflyl product **97**, isolated in 52 % yield. The base was changed to *n*-BuLi and this still resulted in selective O functionalisation but with reduced reaction conversion (90 %). These results suggest that reaction at oxygen is a general feature of the chemistry of pyrazolidinones when using sulfur centered electrophiles.



Scheme 2.11: *Reagents and conditions*: i) NEt_3, CH_2Cl_2, then triflic anhydride, -78 ºC to rt (52 %), or *n*-BuLi, CH_2Cl_2, then triflic anhydride, -78 ºC to rt.

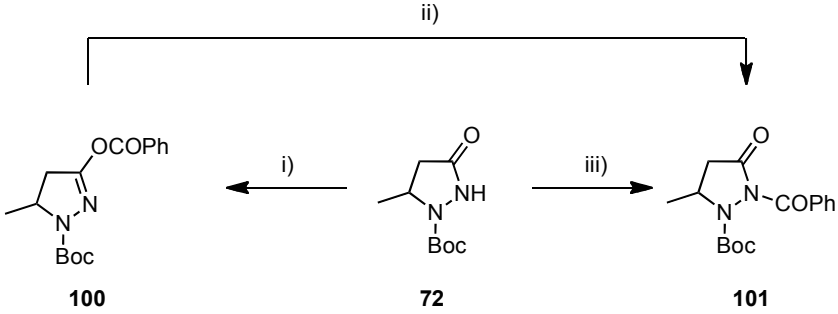
In a further attempt to facilitate N(2) substitution, it was decided to change to carbon-centered electrophiles.[79] Using benzyl chloroformate as the electrophile, analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed 81 % conversion of starting material to

O functionalised compound **98** when using triethylamine as base (Scheme 2.12).[78] **98** was unstable on exposure to silica and could not be isolated by column chromatography, returning only parent compound **72**. Therefore, **98** was characterised as the crude reaction product. However, performing the same reaction with sodium hydride as base allowed for exclusive N(2) functionalisation, with the product **99** isolated in 41 % yield after chromatography on silica. The benzyl carbonate group could also be selectively introduced at nitrogen using the precedented potassium carbonate/DMF conditions, as judged by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. However, as sufficient material was already available, **99** was not isolated in this case.



Scheme 2.12: *Reagents and conditions*: i) NEt_3, CH_2Cl_2, then benzyl chloroformate, -78 ºC to rt; ii) NaH, CH_2Cl_2, then benzyl chloroformate, -78 ºC to rt (41 %), or benzyl chloroformate, DMF, K_2CO_3, rt.

With benzoyl chloride as the electrophile, the use of triethylamine as base gave quantitative conversion to *O*-benzoyl compound **100** (Scheme 2.13). As with *O*-benzyloxycarbonyl carbonate **98**, **100** was not stable to column chromatography so was characterised from the crude reaction product. Interestingly, the use of sodium hydride as base also gave exclusively reaction at oxygen with this electrophile. However, refluxing **100** in toluene gave clean rearrangement to the desired *N*(2)-benzoyl compound **101** in an isolated yield of 45 % from **72**.[79] Alternatively, **101** could be accessed directly using *n*-BuLi as base, albeit with low conversion (50 %), giving 23 % isolated yield of **101** after column chromatography. The regiochemistry of **101** was confirmed by obtaining the crystal structure (Figure 2.11).



Scheme 2.13: *Reagents and conditions*: i) NEt_3, CH_2Cl_2, then benzoyl chloride, -78 ºC to rt, or NaH, CH_2Cl_2, then benzoyl chloride, -78 ºC to rt; ii) toluene, reflux (45 % from **72**); iii) *n*-BuLi, CH_2Cl_2, then benzoyl chloride, -78 ºC to rt (23 %).

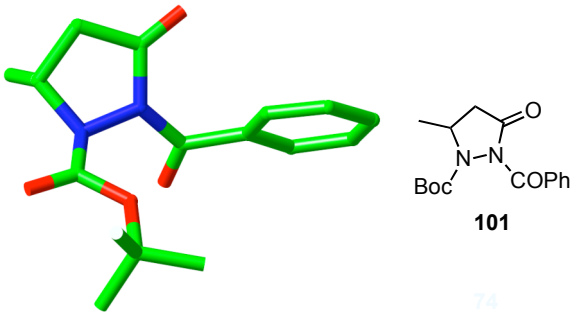
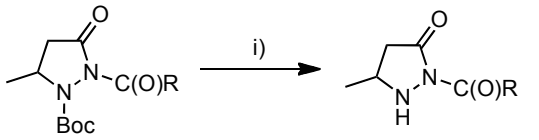


Figure 2.11: Molecular representation of single crystal structure of **101**

With *N*(2)-benzyloxycarbonyl and *N*(2)-benzoyl compounds **99** and **101** in hand, *N*-Boc deprotection of both substrates with trifluoroacetic acid, followed by basic work-up gave the amines **102** and **103**, respectively, in good yield (Scheme 2.14).



99 R = OBn
101 R = Ph

102 R = OBn (78 %)
103 R = Ph (86 %)

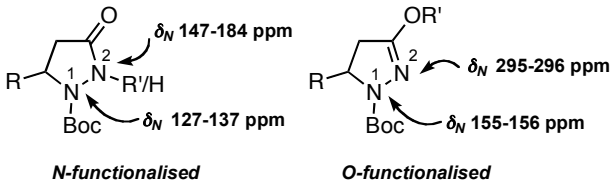
Scheme 2.14: *Reagents and conditions*: i) TFA, CH_2Cl_2, rt, then saturated $NaHCO_3$ solution, CH_2Cl_2.

In summary, a route to the synthesis of a range of substituted pyrazolidin-3-ones, utilising the conjugate addition/cyclisation of hydrazine to an α,β-unsaturated ester as the key step, was developed. This synthetic route was applied to the synthesis of a small range of compounds with a common *N*(2)-benzyl substituent and either methyl, phenyl, *iso*-propyl or trifluoromethyl substitution at C(5). It was found that carbon-centered electrophiles could be used to introduce different substituents at the N(2) position while sulfur-centered electrophiles gave exclusively functionalisation of the oxygen at C(3).

2.3.1 Identification of regioselectivity of O or N(2) functionalisation by ^{15}N NMR spectroscopic analysis

^{15}N NMR spectroscopy was used to confirm the regiochemistry of several of the above products.[80,81] ^{15}N Chemical shifts for a selection of oxygen and nitrogen functionalised compounds were obtained experimentally by ^{1}H,^{15}N HMBC and also calculated at the B3LYP/6-31G* level of theory (Table 2.1). In the case of N functionalised compounds **85**, **74**, **99** and **101** (entries 1, 2, 5 and 6), the N(2) atom has three substituents and shows sp^3 character, while in O-functionalised compounds **96** and **98** (entries 3 and 4), the N(2) atom has two substituents and sp^2 character. This change results in O-functionalised compounds showing a significant downfield shift of the corresponding ^{15}N resonance relative to N-substitution by

around 140 ppm, allowing the N(2) chemical shift to be used as a simple diagnostic tool. In contrast, there is no change in the hybridization of N(1) in all compounds and therefore its ^{15}N chemical shift variation is only marginal (29 ppm). Compounds **96** (entry 3) and **98** (entry 4) are structurally similar to cyclic hydrazones and the chemical shift of the N(2) nitrogens is consistent with the imine nitrogen of a hydrazone moiety.[80] The calculated values are slightly overestimated with an average deviation of 11.7 ppm but, nonetheless, there is good agreement between the experimental and theoretical data.



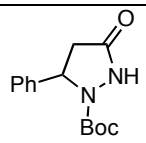
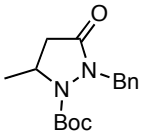
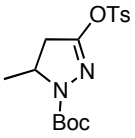
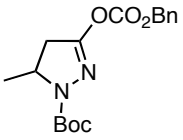
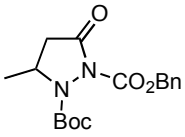
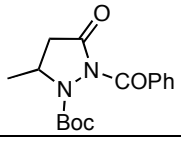
Entry	Compound	Structure	Experimental (ppm) N(1)	Experimental (ppm) N(2)	B3LYP/6-31G* (ppm) N(1)	B3LYP/6-31G* (ppm) N(2)
1	**85**		127	147	139.9	147.7
2	**74**		136	156	143.8	171.6
3	**96**		156	295	170.1	311.7
4	**98**		155	296	165	298
5	**99**		137	166	146.5	183.8
6	**101**		136	184	145	201.1

Table 2.1: ^{15}N NMR experimental and theoretical data for selected compounds

2.3 Dimethylation of catalyst precursors

A variation to the standard pyrazolidinone architecture previously discussed is the introduction of a *gem*-dimethyl group at the C(4) position of the heterocyclic system (Figure 2.12). It was envisaged that these groups would fix the orientation of any adjacent stereodirecting groups

present.[60] This may aid stereoselectivity in reactions using enantiomerically pure catalysts and facilitate efficient transfer of chiral information from the catalyst to the substrate. Furthermore, the introduction of a *gem*-dimethyl group blocks any possible enolisation at C(4) of the catalyst.

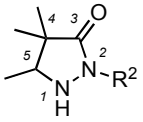
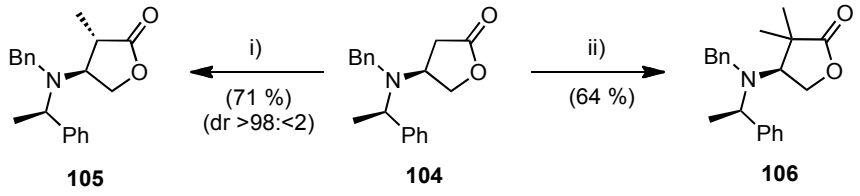


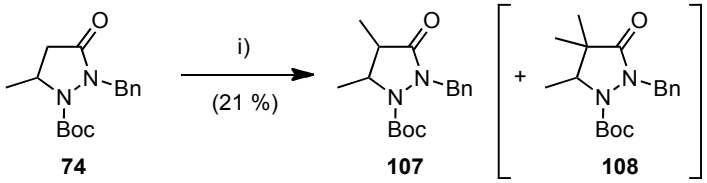
Figure 2.12: Structure of potential *gem*-dimethyl substituted pyrazolidinone catalyst

It has been reported by Davies *et al.* that γ-butyrolactones, such as **104,** could be either mono- or dialkylated (**105** and **106**, respectively) by treatment with differing quantities of KHMDS and iodomethane. Monoalkylation proceeded with high levels of diastereoselectivity (Scheme 2.15).[82]



Scheme 2.15: Reagents and conditions: i) 1.2 eq KHMDS, -78 ºC, THF, then 5.0 eq CH_3I, -78 ºC to rt; ii) 5.0 eq KHMDS, -78 ºC, THF, then 10 eq CH_3I, -78 ºC to rt.

Conditions for monomethylation were applied to substrate **74** and this resulted in a mixture of residual starting material, monomethylated product **107** and a small amount of the dimethylated compound **108** in the ratio 40:48:12 (**74**:**107**:**108**), as judged by ^{1}H NMR spectroscopic analysis (Scheme 2.16). The monomethylated product was a mixture of diastereoisomers in the ratio 90:10, however, the relative configuration within these diastereoisomers (either *syn* or *anti*) was not unambiguously established. The quoted yield of 21 % is the isolated yield of the major diastereoisomer of **107** as the minor diastereoisomer could not be separated by column chromatography from dimethylated compound **108**.

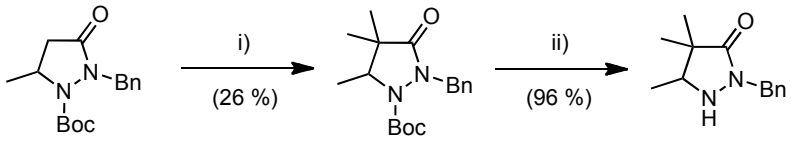


Scheme 2.16: *Reagents and conditions*: i) 1.2 eq KHMDS, -78 ºC, THF, then 5.0 eq CH_3I, -78 ºC to rt.

Although the dimethylated compound **108** was only obtained in small amounts in this reaction, it was encouraging that dimethylation was possible under conditions only intended for monomethylation. To increase conversion to dimethylated product, the reaction was repeated with an increased excess of both KHMDS and iodomethane (5.0 and 10 equivalents,

respectively) in an attempt to force full alkylation (Scheme 2.17). However, analysis of the ^{1}H NMR spectrum of this crude reaction mixture again showed a mixture of starting material **74**, monomethylated material **107** and dimethylated product **108** in the ratio 27:44:29 (**74**:**107**:**108**). Hence, this mixture was retreated with the same conditions as before and, with this extra encouragement, an improved **74**:**107**:**108** ratio of 8:11:81 was achieved. The final isolated yield, after purification, was significantly lower than this (26 %), presumably indicating some unspecified decomposition under these relatively forcing conditions. These reactions have not been repeated and require further optimisation.

With this material in hand, it was then possible to *N*-Boc-deprotect substrate **108** by treatment with trifluoroacetic acid and liberate the free amine **109** by basic work-up in high yield (Scheme 2.17). Compound **109** was taken on for further testing.



74 **108** **109**

Scheme 2.17: *Reagents and conditions*: i) 5.0 eq KHMDS, -78 ºC, THF, then 10 eq CH_3I, -78 ºC to rt, then 5.0 eq KHMDS, -78 ºC, THF, then 10 eq CH_3I, -78 ºC to rt; ii) TFA, CH_2Cl_2, rt, then saturated $NaHCO_3$ solution, CH_2Cl_2.

2.4 Testing of pyrazolidinones as organocatalysts

2.4.1 Proof of concept reactions

Having developed a synthetic route to a variety of pyrazolidin-3-ones, verification of their ability to act as organocatalysts in the Diels-Alder reaction of (*E*)-cinnamaldehyde **37** and cyclopentadiene was tested. *C*(5)-methyl, *N*(2)-benzyl compound **76** was used as a model catalyst and tested with a selection of conditions employed with related literature catalysts (Table 2.2). All reactions were carried out at 20 mol% catalyst loading ([0.19 M] catalyst concentration) and analysed after 42 h by ^{1}H NMR spectroscopy. The first set of conditions, triflic acid as co-catalyst in water, mimicked those of Ogilvie and Lemay (entry 1).[67] Turnover was observed but reaction was sluggish, giving only 22 % conversion in 42 h. Markedly improved conversion was observed using hydrochloric acid as co-catalyst in methanol, in analogy to conditions employed by Tomkinson *et al.* (entry 2).[64] The use of triflic acid with methanol gave a further small improvement in turnover (entry 3). In all cases, the catalysts showed significant *exo* diastereoselectivity. It should be noted that reactions in methanol resulted in the formation of a mixture of the dimethyl acetals **110**, ***exo*-111** and ***endo*-111** and

the corresponding aldehydes (Figure 2.13). Hence, analysis by ^{1}H NMR spectroscopy was preceded by hydrolysis with trifluoroacetic acid to give only the respective aldehydes.

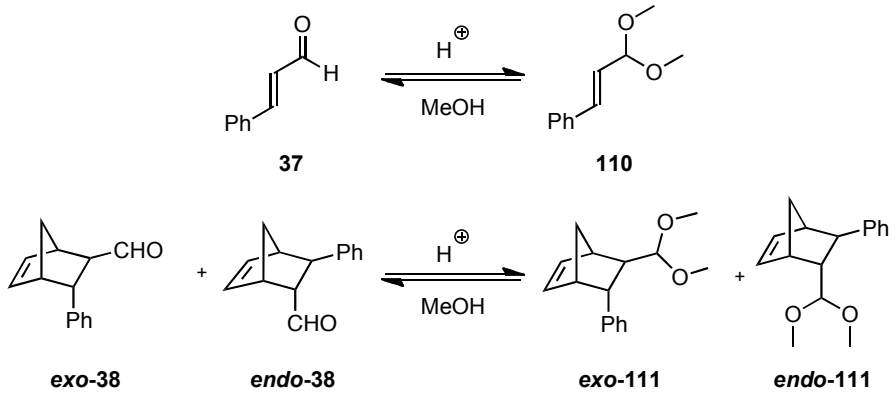
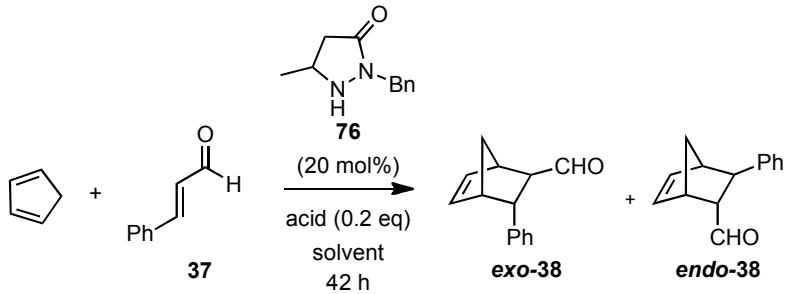


Figure 2.13: Equilibria of dimethyl acetals to aldehyde

For entries 2 and 3, conversion is also represented by a $t^{1/2}$ value (time to reach 50 % conversion). These were obtained by taking reaction aliquots that were then hydrolysed before analysis by ^{1}H NMR spectroscopy to establish conversion and the ratio of diastereoisomeric products ***exo*-38** and ***endo*-38**. This ratio of diastereoisomers remained essentially constant for all reactions in this report that were analysed by this method and so only a single value is given in all cases.

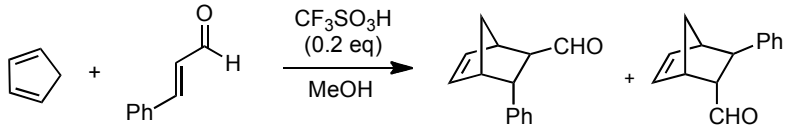


Entry	Solvent	Acid	Conversion (%)	$t^{1/2}$ (h)	*exo: endo*
1	water	CF_3SO_3H	22	-	63:47
2	MeOH	HCl	48	45	74:26
3	MeOH	CF_3SO_3H	65	40	72:28

Table 2.2: Solvent and acid screen with catalyst **76**

On the basis of the above results, it was decided to employ methanol as solvent and triflic acid as co-catalyst for subsequent studies into the effect of the catalyst architecture on reactivity and diastereoselectivity. A reaction without pyrazolidinone catalyst was then run to establish the rate of background reaction (Figure 2.14). Interestingly, triflic acid in isolation was found to be a more active catalyst than in combination with **76**, giving a $t^{1/2}$ of 10 h and a markedly different diastereoselectivity of 14:86 *exo*:*endo*. This result indicated that triflic acid itself was not

available to catalyse the cycloaddition in the presence of a pyrazolidinone, potentially as a result of iminium formation.



37 ***exo*-38** ***endo*-38**

$t^{1/2}$ 10 h, *exo:endo* 14:86

Figure 2.14: Background reaction of triflic acid in methanol

2.4.2 Model studies

Having established that pyrazolidin-3-ones can catalyse the Diels-Alder cycloaddition of (*E*)-cinnamaldehyde and cyclopentadiene, the next stage was to investigate how substitution on the pyrazolidinone ring influenced the reaction in terms of reaction rate and diastereoselectivity. Reactions were monitored by reaction sampling, hydrolysis and analysis by ^{1}H NMR spectroscopy to obtain $t^{1/2}$ values. The reaction conditions of 20 mol% [0.19 M] catalyst loading and 20 mol% triflic acid in methanol were used consistently.

2.4.2.1 C(4) and C(5) substitution

Figure 2.15 outlines $t^{1/2}$ values and diastereoselectivities observed with a range of C(4) and C(5) substituted catalysts all carrying a common *N*(2)-benzyl substituent. The introduction of a *gem*-dimethyl group at C(4) (catalyst **109**) gave a significant rate acceleration over *C*(4)-unsubstituted compound **76** with $t^{1/2}$ reduced to 5 h. However, this acceleration came at the expense of diastereoselectivity, with the *endo* diastereoisomer only marginally preferred to the *exo* (*exo*:*endo* 46:54).

The nature of the C(5) substituent also had a significant effect upon reaction rate. The use of either *C*(5)-phenyl or *C*(5)-trifluoromethyl substituted catalysts **91** and **93** gave the highest rates ($t^{1/2}$ 5 h and 6 h, respectively). Catalysts **76** and **92**, both of which contain *C*(5)-alkyl substitution are significantly slower. The C(5) substituent also had an effect on diastereoselectivity. Compounds **91** and **76** displayed high selectivity for the *exo* diastereoisomer (73:27 and 72:28, respectively). In contrast, catalyst **93** showed a significant reversal of diastereoselectivity, favouring the *endo* diastereoisomer, with an *exo*:*endo* ratio of 35:65.

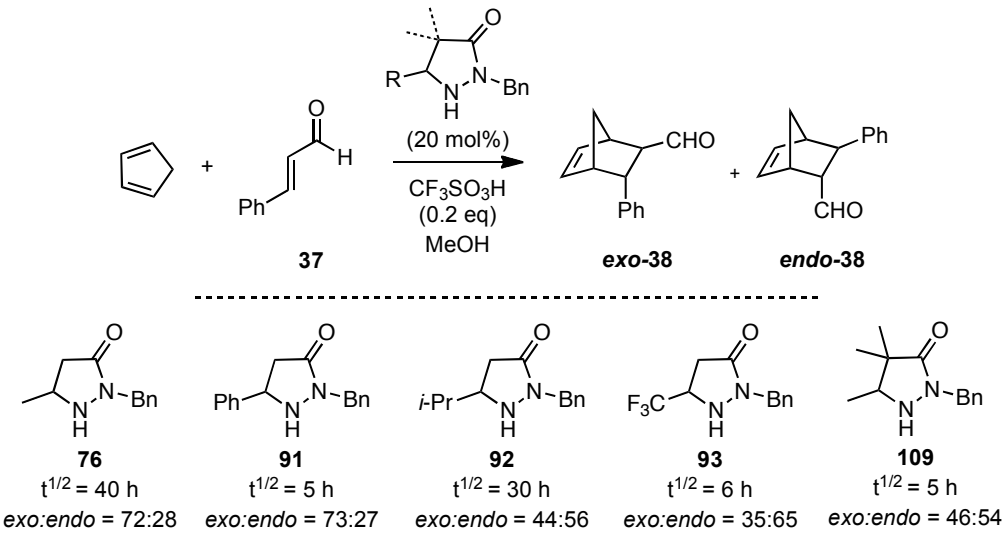


Figure 2.15: Variation of C(4) and C(5) substitution and on reaction rate and diastereoselectivity

2.4.2.2 N(2) substitution

In order to explore the effects of N(2) substitution, testing of a range of racemic *C*(5)-methyl substituted pyrazolidinones bearing both alkyl (Me, Bn) and electron-withdrawing groups (CO_2Bn, COPh) at the N(2) position were evaluated (Figure 2.16). In the *N*(2)-alkyl series, the reaction catalysed by the *N*(2)-methyl substituted catalyst **67** gave a greater rate of reaction relative to the *N*(2)-benzyl substituted compound **76**. It had been shown in analogous systems that the introduction of a β-electron withdrawing group, with respect to the reactive amine centre, led to a significant improvement in the observed reaction rate.[63,64] This also proved to be a general feature of the pyrazolidinone motif with the most effective catalysts in this series, in terms of reaction rate, being compounds **102** and **103**. Of these, compound **102** displayed the highest turnover of all the catalysts tested to date, with the reaction reaching 50 % conversion in 2 h. Compounds **102** and **103** also displayed similar levels of diastereoselectivity, favouring the *exo* diastereoisomer by ratios of 63:37 and 59:41, respectively. Compound **67** showed a small selectivity for the *endo* diastereoisomer (44:56 *exo*:*endo*), in contrast to the other catalysts tested in this series.

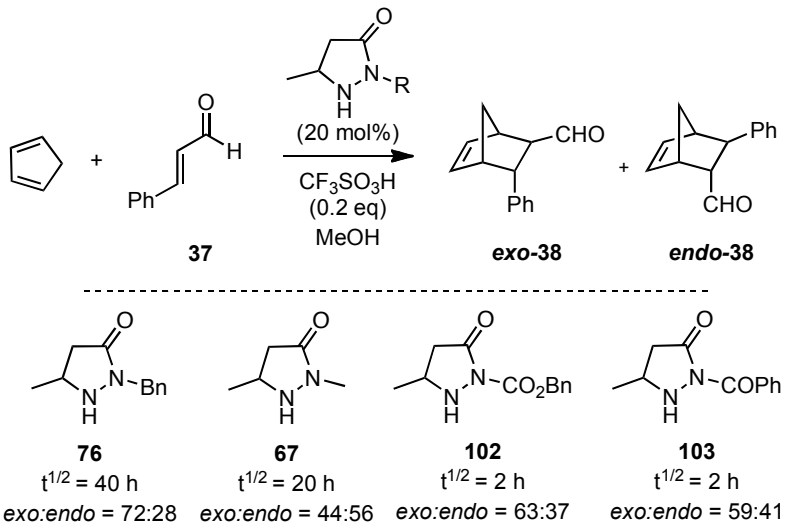
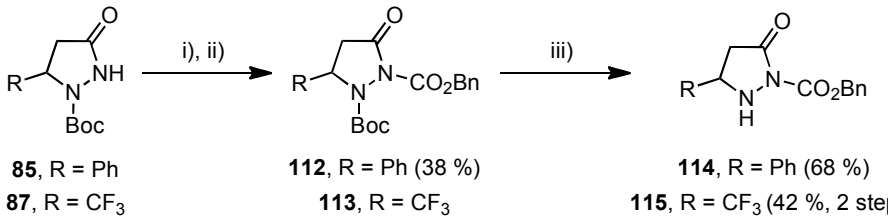


Figure 2.16: Variation of N(2) substitution and on reaction rate and diastereoselectivity

2.4.2.3 Catalyst optimisation

In an attempt to further optimise catalyst efficiencies, the incorporation of a *C*(5)-phenyl or *C*(5)-trifluoromethyl group, in combination with an electron-withdrawing *N*(2)-carboxybenzyl substituent, was evaluated. Following the methodology developed previously, **114** and **115** were prepared from **85** and **87**, respectively (Scheme 2.18).



Scheme 2.18: *Reagents and conditions*: (i) NaH, CH_2Cl_2, then benzyl chloroformate, −78 ºC to rt; (ii) toluene, reflux; (iii) TFA, CH_2Cl_2, rt then saturated $NaHCO_3$ solution, CH_2Cl_2.

The regiochemistry of the *N*(2)-carboxylation of **85** was confirmed by ^{15}N NMR spectroscopy (Figure 2.17). The chemical shifts for both Boc-protected **112** and final catalyst **114** were obtained and found to be in good agreement with calculated values.

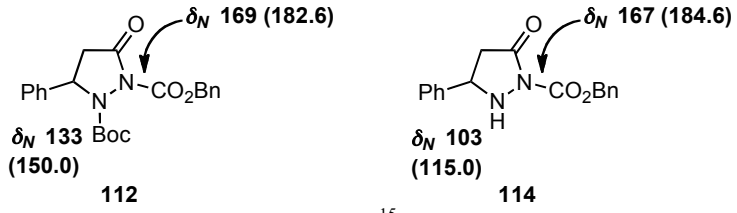


Figure 2.17: Theoretical and experimentally determined ^{15}N NMR spectroscopic data (in ppm) for **112** and **114** (theoretically determined values in parentheses)

These compounds were subsequently evaluated as catalysts for the Diels-Alder reaction- both were highly active with *C*(5)-phenyl **114** giving the best catalytic efficiency observed within

this series of catalysts ($t^{1/2}$ 1 h, Figure 2.18). Modest *exo* diastereoselectivity was observed with this catalyst while *C*(5)-trifluoromethyl **115** showed no selectivity.

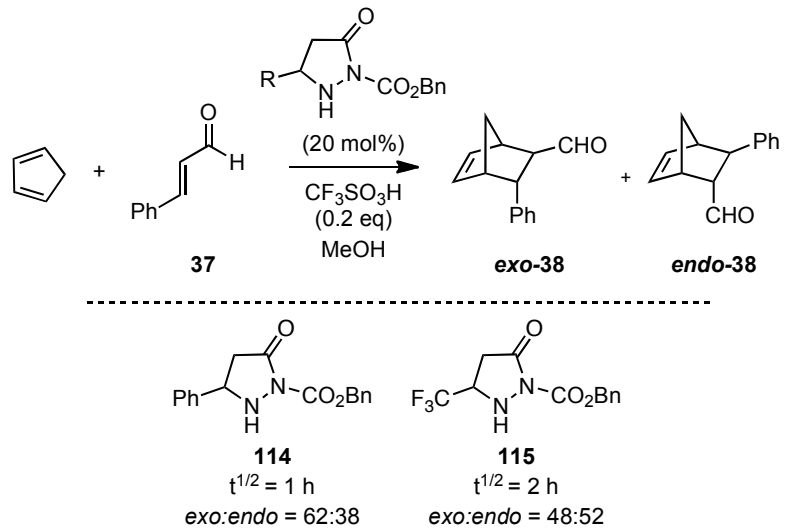


Figure 2.18: Variation of C(5) substitution on reaction rate and diastereoselectivity of *N*(2)-carboxybenzyl catalysts

At the end of analysis of catalyst structure, it was found that the incorporation of an electron-withdrawing *N*(2)-carboxybenzyl group and either a *C*(5)-phenyl or trifluoromethyl unit within the pyrazolidinone template led to increased catalytic activity. Diastereoselectivity varied significantly, with *C*(5)-trifluoromethyl, *N*(2)-benzyl catalyst **93**, in particular displaying significant *endo* diastereoselectivity, an unusual feature for an organocatalyst which normally show dominant *exo* diastereoselectivity (Figure 2.19).[48,83] Catalysts **93** and **114** were taken forward for substrate screening.

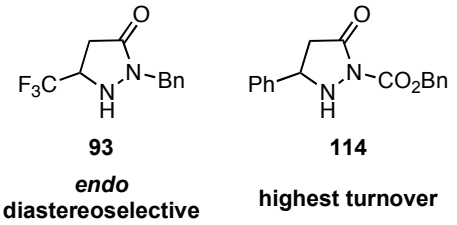


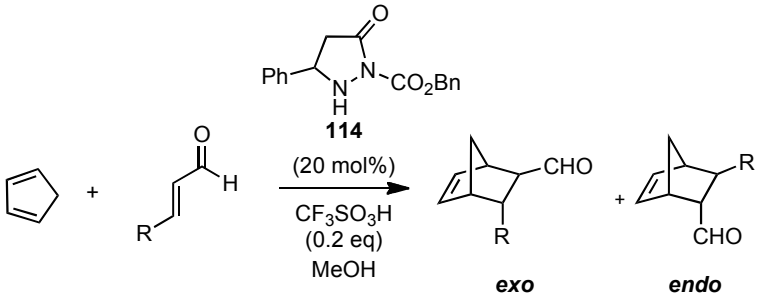
Figure 2.19: Catalysts taken forward for substrate screen

2.5 Substrate screening of catalysts 93 and 114

2.5.1 Variation of dienophile

We began by evaluating the substrate scope of **114** in the organocatalytic Diels-Alder reaction with regards to the aldehyde (Table 2.3). Catalyst **114** displayed good reactivity for the reactions of cinnamaldehyde, 4-nitrocinnamaldehyde and hexen-2-al with cyclopentadiene, furnishing the desired products in good isolated yields and modest *exo* diastereoselectivity (entries 1-3). Short reaction times indicated the high reactivity of the catalyst. A longer reaction

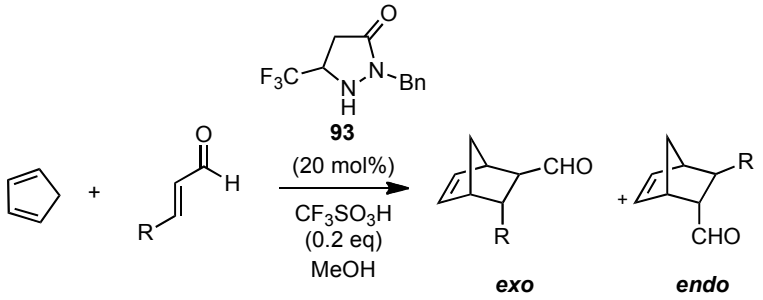
time of 24 h was necessary when ester substitution was incorporated and no diastereoselectivity was observed (entry 4).



Entry	R	Time (h)	Yield (%)	*exo:endo*
1	Ph	7	89	62:38
2	4-NO_2-C_6H_4	5	73	65:35
3	*n*-Pr	4	75	58:42
4[a]	CO_2Et	24	80	50:50

Table 2.3: Substrate tolerance of catalyst **114** in Diels-Alder reactions
a) 5 % water added

Catalyst **93** was also further evaluated to see whether *endo* diastereoselectivity was observed with substrates other than cinnamaldehyde (Table 2.4). An *exo*:*endo* ratio of 36:64 was also observed when hexen-2-al was utilised (entry 2). As expected, longer reaction times were required with both substrates to achieve good conversion.



Entry	R	Time (h)	Yield (%)	*exo:endo*
1	Ph	48	50	22:78
2	*n*-Pr	6	67	36:64

Table 2.4: Testing of *endo*-selective catalyst **93** with a range of substrates

2.5.2 Variation of diene

We next examined the diene substrate scope of catalyst **114**. It has been found that the reactivity of iminium ion catalysed Diels-Alder reactions with dienes other than cyclopentadiene are strongly dependent on a suitable substrate/ diene combination.[84,85] The organocatalysed reaction between aldoester **116** and either isoprene or 2,3-dimethylbuta-1,3-diene has been reported by Hayashi and co-workers[45,83] but either combination with *C*(5)-phenyl catalyst **114** returned only starting material after 24 h (Figure 2.20). A change to more reactive (*E*)-cinnamaldehyde **37**

again returned only starting material with both isoprene and cyclohexadiene after overnight reaction.

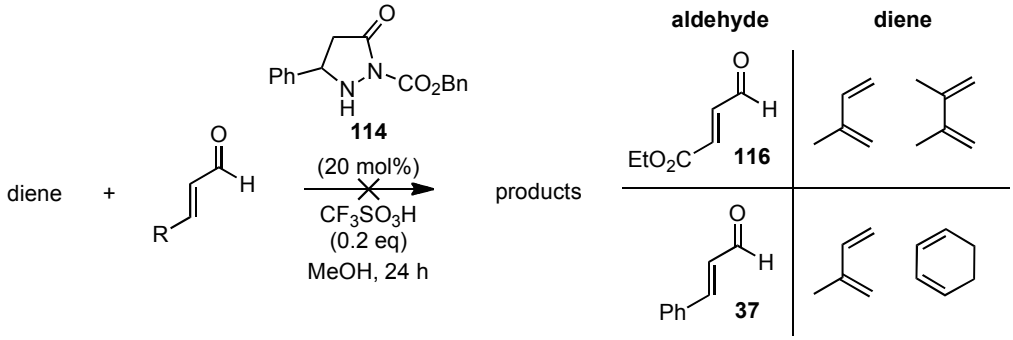
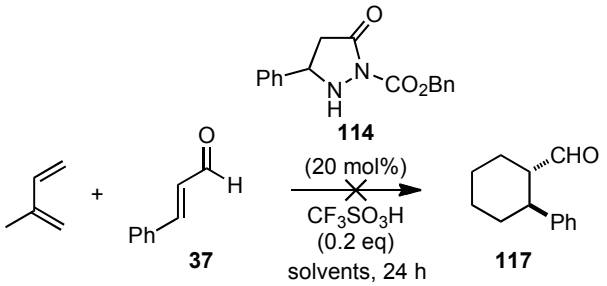


Figure 2.20: Unsuccessful aldehyde/diene combinations

In an attempt to overcome this lack of reactivity, a brief solvent screen was undertaken for the reaction of cinnamaldehyde **37** and isoprene (Figure 2.21). The systems selected were all utilised by MacMillan while screening his chiral imidazolidinone catalyst, albeit with different substrate combinations.[1] However, all were unsuccessful and returned unreacted aldehyde.



Solvents tested = MeOH, MeCN:H_2O (95:5) or DMF:H_2O (95:5)
Figure 2.21: Solvent screening for reaction of **114** with isoprene

As a final alternative, *C*(5)-trifluoromethyl catalysts **93** and **115** were tested in the reaction of (*E*)-cinnamaldehyde **37** and cyclohexadiene (Figure 2.22). In both cases, starting material was returned after 24 h. Due to time constraints, other conditions, such as the use of alternative aldehyde/ diene combinations, were not explored.

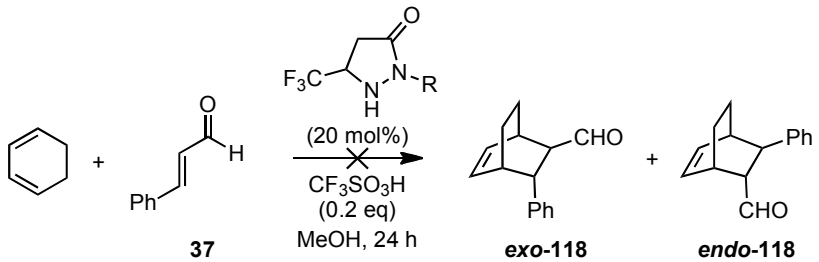


Figure 2.22: Reaction of *C*(5)-trifluoromethyl catalysts **93** (R = Bn) and **115** (R = CO_2Bn) with (*E*)-cinnamaldehyde **37** and cyclopentadiene

2.6 Summary

A route for the synthesis of racemic pyrazolidinones allowing ready access to different C(5) and N(2) substituent combinations was successfully developed. This chemistry was then applied to the synthesis of a series of *N*(2)-benzyl pyrazolidinones and a series of *C*(5)-methyl pyrazolidinones and these compounds screened in the Diels-Alder cycloaddition of (*E*)-cinnamaldehyde **37** and cyclopentadiene. In terms of reactivity, *C*(5)-phenyl or trifluoromethyl and *N*(2)-carboxybenzyl substitution were optimal. *C*(5)-Phenyl, *N*(2)-carboxybenzyl catalyst **114** was screened against a small range of α,β-unsaturated aldehydes and showed good reactivity. *C*(5)-Trifluoromethyl, *N*(2)-benzyl catalyst **93** showed unusual *endo* diastereoselectivity in the reactions of both cinnamaldehyde and hexen-1-al. Neither catalyst, however, gave any conversion when reaction was attempted with dienes other than cyclopentadiene.

Chapter 3: Resolution of racemic pyrazolidin-3-ones for the synthesis of a chiral organocatalyst

This chapter details the development of a method for the synthesis of enantiomerically pure pyrazolidin-3-one catalysts by resolution. The amide coupling of *C*(5)-phenyl pyrazolidinone **83** to a selection of chiral acids was explored using a range of conditions. The regioselectivity of this amide coupling was unambiguously determined by a combination of X-ray crystal structure data and ^{15}N NMR spectroscopy. The optimal conditions found were the use of (*R*)-methylmandelic acid, two equivalents of coupling agents EDCI and HOBt, DMF as solvent and a delay of 5 minutes before addition of pyrazolidinone **83**. The resultant diastereoisomers could be separated by chromatography and the acid portion removed by refluxing in 6 M hydrochloric acid to give enantioenriched **(*R*)-83**. **(*R*)-83** was elaborated to catalyst **(*R*)-114** which was found to give diastereoisomeric products ***exo*-(2*R*)-38** and ***endo*-(2*R*)-38** in 48 % and 28 % ee, respectively.

3.1 Strategies for resolution of pyrazolidinone 83

In our efforts to develop an asymmetric iminium ion organocatalyst, the initial target was enantioenriched compound **114** (Figure 3.1) as this was the most effective catalyst, in terms of reaction rate, evaluated at this stage. Two strategies were envisaged that would allow access to this compound, starting from the previously described racemic precursor **83**. The first was to achieve separation *via* selective crystallisation of a single enantiomer using a chiral acid. The second would involve direct reaction with a chiral acid derivative to give a pair of diastereoisomeric amides, which could then be separated by column chromatography and/or recrystallisation. It was initially assumed that the reaction of **83** with a chiral acid derivative would exclusively take place through the amine nitrogen at N(1), in analogy to the selective reaction with di-*tert*-butyl dicarbonate observed in the synthesis of compound **85** (see Scheme 2.7). It was later established that the major product in nearly all cases was the corresponding N(2)-functionalised analogue shown. This will be discussed in detail in Section 3.3.3.4.

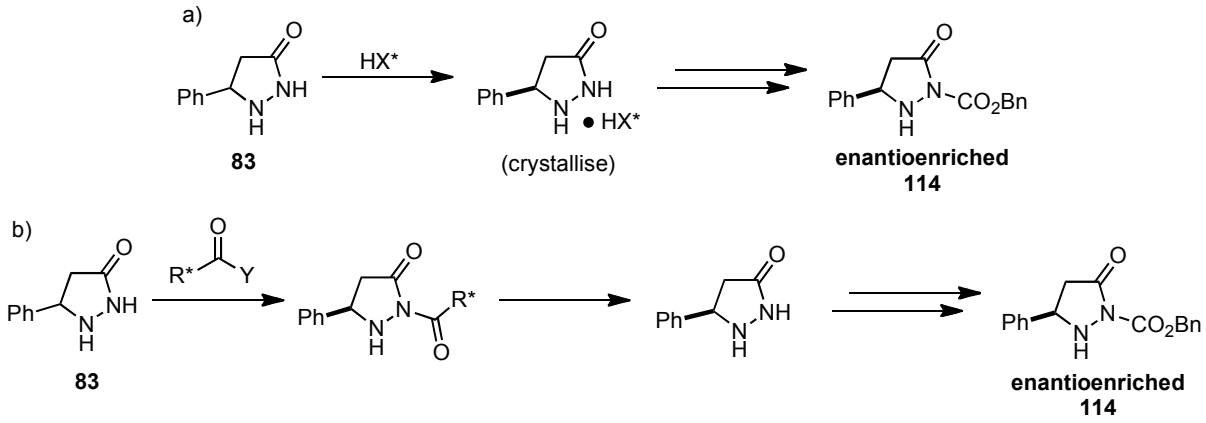


Figure 3.1: Strategies for resolution of compound **83**

3.2 Resolution of pyrazolidinone 83 by crystallisation of a chiral salt

The first method investigated was selective crystallisation using a chiral acid. When a racemic mixture of a basic compound is treated with a chiral acid, a pair of diastereoisomeric salts are formed (Figure 3.2). As diastereoisomers, these two salts have different physical properties and, therefore, it may be possible to selectively crystallise one over the other with high levels of selectively.[86] Subsequent neutralisation should return the parent compound in enantioenriched form.

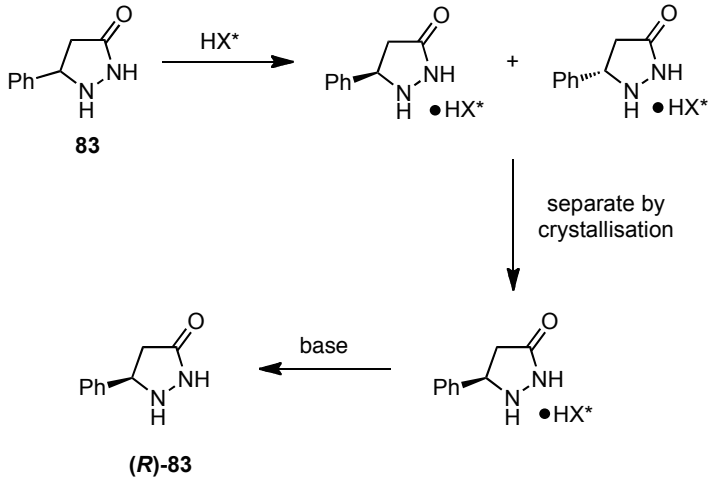


Figure 3.2: Resolution of compound **83** by selective crystallisation of diastereoisomeric salts

In order to find a suitable set of conditions for the selective crystallisation of one enantiomer of compound **83** it was first necessary to establish which chiral acids were capable of protonating **83** and thus form a salt. Figure 3.3 shows the chiral acids tested for salt formation with compound **83** by the addition of one equivalent of acid to one equivalent of **83** in deuterated chloroform. Of these, only (+)-camphor sulfonic acid **124** and (-)-1,1'-binaphtyl-2,2'-diyl hydrogenphosphate **125** were sufficiently strong acids to protonate **83**, as judged by chemical

shift changes in the ^{1}H NMR spectra.

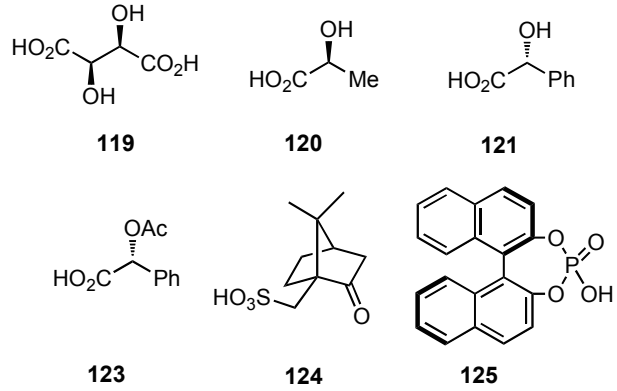
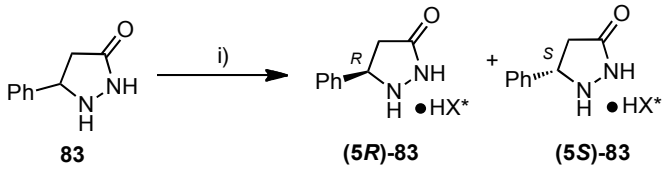


Figure 3.3: Compounds tested for salt formation with **83**

These two acids were then tested in a small range of solvents, such as diethyl ether and THF, in order to ascertain whether it was possible to crystallise a salt composed of a single enantiomer of **83** (Scheme 3.1). Half an equivalent of acid was used in this case in order to encourage the crystallisation of one enantiomer and not a mixture of diastereoisomeric salts. Unfortunately, no crystallisation was observed either at room temperature or on cooling to 0 ºC. This method of resolution was not advanced further.



Scheme 3.1: *Reagents and conditions*: i) 0.5 eq (+)-camphor sulfonic acid **124** or (-)-1,1'-binaphtyl-2,2'-diyl hydrogenphosphate **125**, diethyl ether or THF, 0 ºC to rt.

3.3 Resolution of pyrazolidinone 83 by formation of diastereoisomeric amides

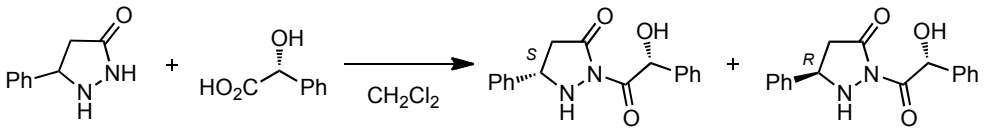
3.3.1 Initial investigations

As an alternative to selective crystallisation, it was envisaged that compound **83** could also be resolved by coupling to a single enantiomer of an appropriate chiral acid or acid derivative. Column chromatography and/or recrystallisation of the resultant diastereoisomers, followed by cleavage of the acid, would then give both enantiomers of **83** in enantioenriched form. Two such strategies tentatively explored were the coupling of **83** to (1*S*)-menthyl chloroformate and (*R*)-α-methylbenzyl isocyanate. In both cases a mixture of diastereoisomeric products were obtained, as judged by ^{1}H NMR spectroscopic analysis. However, in both cases no separation of the products could be observed by TLC analysis and these routes were not explored further. The mixtures of diastereoisomeric products were not characterised.

3.3.2 Direct chiral acid coupling

Another possibility was coupling of **83** to a chiral acid directly, making use of a selection of the many coupling agents now commercially available for the activation of acids in such amide bond-forming reactions.[87] (*R*)-Mandelic acid **126** was initially chosen as the acid substrate for these reactions because it is a readily manipulated solid and was commercially available in enantiomerically pure form.

The direct coupling of (*R*)-mandelic acid **126** with amine **83**, facilitated by a range of coupling agents is outlined in Table 3.1. Reactions were left overnight at room temperature before work-up and the crude material examined by either ^{1}H NMR spectroscopy or HPLC analysis to establish whether product formation had taken place. The majority of reaction conditions (entries 1-6) showed little or no conversion to products, instead giving complex mixtures of unidentified components. Interestingly, the combination of EDCI and DMAP in dichloromethane showed no evidence of product formation (entry 6) while EDCI and HOBt gave an isolated yield of the combined diastereoisomers of 33 % (entry 7). It was established from this reaction that **(5*S*)-** and **(5*R*)-127** could be readily separated by column chromatography, utilising an ethyl acetate/petrol eluent system. Separation by this method gave clean samples of compounds **(5*S*)-** and **(5*R*)-127** in 13 and 15 % yield, respectively, after a single column. The combination of PyBOP and Hunig's base also gave **(5*S*)-** and **(5*R*)-127**, albeit in a lower yield of 20 % (entry 8). Hence, the reaction with EDCI and HOBt was chosen for further optimisation.



83 **126** **(5*S*)-127** **(5*R*)-127**

Entry	Reagents	Product Observed?
1[a]	DCC, DMAP	No
2[b]	HATU, NEt_3	No
3[b]	HBTU, NEt_3	No
4[b]	BOP, NEt_3	No
5[b]	Cyclophos, NEt_3	No
6[a]	EDCI, DMAP	No
7[a]	EDCI, HOBt	Yes (32 %)
8[a]	PyBOP, $(i\text{-Pr})_2NEt$	Yes (20 %)

Table 3.1: Screening of peptide coupling conditions
a) Analysed by ^{1}H NMR spectroscopy b) Analysed by HPLC

3.3.3 Optimisation

3.3.3.1 Variation of reaction conditions using (*R*)-mandelic acid 126

It was now established that racemic pyrazolidinone **83** could be coupled to chiral mandelic acid and the resulting diastereoisomers separated. The yield, however, was only 33 % and it was hoped to improve on this initial figure by optimisation of the reaction conditions. This began by screening to find the ideal solvent for the reaction (Table 3.2). The use of THF gave essentially identical yield to the use of dichloromethane (entry 2) whereas the use of DMF led to a small increase in yield from 32 to 40 % (entry 3). Also, for reaction in THF, addition of **126** five minutes after the other reagents was beneficial, with the yield increasing by 7 % (entries 2 and 4). This was presumably due to the increased concentration of the desired activated acid intermediate **128** (Figure 3.4).

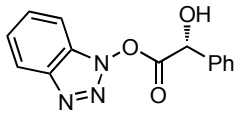
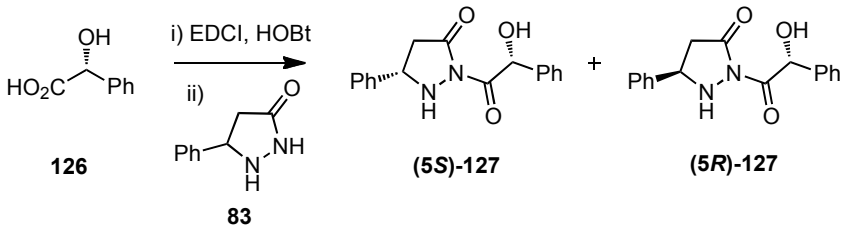


Figure 3.4: Activated acid intermediate **128**

Interestingly, increasing the time before addition of **126** to 2 h led to a large drop in yield to just 7 % suggesting the concentration of intermediate **128** may peak then drop-off over time (entry 5). Increasing the number of equivalents of acid **126**, EDCI and HOBt also led to a

further increase in yield to 47 %, although this represents a rather modest improvement considering the large increase in reagents (entry 6). As the EDCI used in the reaction was the hydrochloride salt, the addition of triethylamine to neutralise this excess acid was also investigated (entry 7). The yield of 26 % showed that the addition provided no benefit to the reaction yield.



126 **83** **(5*S*)-127** **(5*R*)-127**

Entry	Solvent	Equiv of EDCI/HOBt	Delay (min)	Yield ((5*S*)- and (5*R*)-127 combined) (%)
1	CH_2Cl_2	1	0	32
2	THF	1	0	33
3	DMF	1	0	40
4	THF	1	5	40
5	THF	1	120	7
6	THF	2	5	47
7[a]	DMF	1	5	26

Table 3.2: Optimisation of amide coupling of pyrazolidinone **83** with (*R*)-mandelic acid **126**
a) 1 eq of NEt_3 also included

In order to further optimise reaction yield, the use of an alternative to HOBt was briefly explored. The screening of reaction conditions had already shown that the reaction was very sensitive to the coupling agents used (see Table 3.1). Hence, it was hoped that more subtle changes to the previously successful combination of EDCI/HOBt would yield greater returns of diastereoisomeric products **(5*S*)-** and **(5*R*)-127**. Ethyl 2-cyano-2-(hydroxyimino)acetate **129**, sold commercially as Oxyma Pure, has been developed as an alternative to HOBt with a similar level of success in peptide couplings (Figure 3.5).[88]

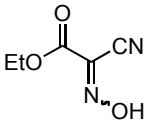
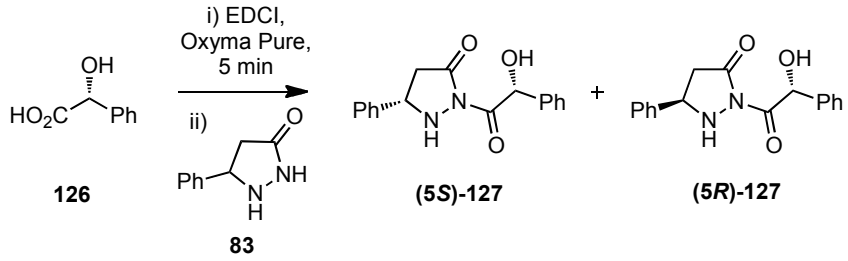


Figure 3.5: Oxyma Pure **129**

Hence, the small-scale coupling of racemic **83** with (*R*)-mandelic acid was attempted, substituting Oxyma Pure **129** for HOBt, in a small range of solvents (Table 3.3). In each case,

the isolated yield compared unfavourably with those obtained with HOBt and this route was not investigated further.



Entry	Solvent	Yield (%)
1	CH_2Cl_2	9
2	DMF	19
3	THF	26

Table 3.3: Screening of Oxyma Pure **129** in a small range of solvents

3.3.3.2 Screening of alternative acid coupling partners

The next stage of optimisation focused on variation of the acid component in the hopes of increasing the overall yield while maintaining efficient separation of the two diastereoisomeric products. There was concern that the alcoholic side-chain of the acid may give rise to significant side-reactions, either by acting as a nucleophile through the alcohol or conversely as an electrophile in S_N2-type reactions (Figure 3.6a)). Hence, the choice of acids focused on compounds in which the alcohol of (*R*)-mandelic acid was either protected or removed altogether, while maintaining a stereocentre α to the acid functionality. To this end, (*R*)-acetylmandelic acid **130**, (*R*)-methylmandelic acid **131** and (*S*)-Naproxen **132** were examined as potential coupling partners (Figure 3.6b)).

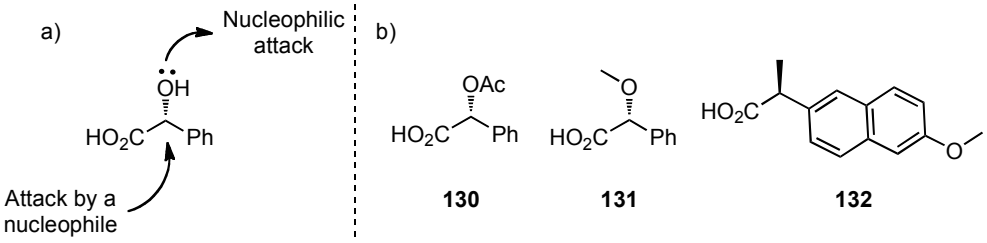
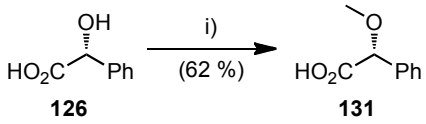


Figure 3.6: a) Potential sites of side-reactions with (*R*)-mandelic acid; b) alternative acid substrates

(*R*)-Acetylmandelic acid **130** and (*S*)-Naproxen **132** were each commercially available and (*R*)-methylmandelic acid **131** was readily synthesised in one step from (*R*)-mandelic acid **126** in 62 % yield (Scheme 3.2). Greater than two equivalents of sodium hydride were used, leading to

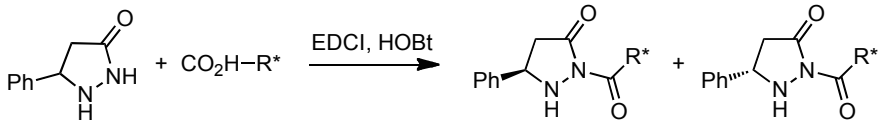
a dianion intermediate which was then selectively methylated at the more reactive alkoxide position.



126 **131**

Scheme 3.2: *Reagents and conditions*: i) 3 eq NaH, THF, 0 ºC, then CH_3I, reflux.

Reaction of amine **83** with the two O-protected derivatives in THF gave similar yields to that of mandelic acid itself (Table 3.4, entries 1 and 2). When the reaction conditions were changed to reflect the results of the optimisation outlined in Section 3.3.3.1 i.e. DMF as solvent and **83** added 5 minutes after the other reagents, a significant improvement in the yield from 29 % to 53 % was observed with (*R*)-methylmandelic acid **131** (entry 3). A similar yield of 54 % was achieved when (*S*)-Naproxen **132** was employed under these conditions (entry 4). The use of a microwave reactor and elevated temperatures has been found to be beneficial in certain amide coupling reactions[89] in terms of both reaction rate and yield and this was tested in this series utilising reaction with (*S*)-Naproxen **132** (entry 5). While it was found that the use of a microwave did allow reaction time to be reduced to just 10 minutes, it was not advantageous in terms of yield, which dropped slightly in comparison to the ambient reaction to 45 %. HPLC analysis of the reaction mixture indicated full consumption of (*S*)-Naproxen **132**, in this case.



83

Entry	Acid	Products	Solvent	Delay (min)	Yield (%)
1	(*R*)-acetylmandelic **130**	**(5*S*)- and (5*R*)-133**	THF	0	36
2	(*R*)-methylmandelic **131**	**(5*S*)- and (5*R*)-134**	THF	0	29
3	(*R*)-methylmandelic **131**	**(5*S*)- and (5*R*)-134**	DMF	5	53
4	(*S*)-Naproxen **132**	**(5*S*)- and (5*R*)-135**	DMF	5	54
5[a]	(*S*)-Naproxen **132**	**(5*S*)- and (5*R*)-135**	DMF	0	45

Table 3.4: Screening of conditions for coupling of 5-phenylpyrazolidin-3-one **83** with different acids
a) Reaction in a microwave reactor at temperature of 100 ºC for 10 min

The absolute configuration and regiochemistry of (*S*)-Naproxen-derived diastereoisomer **(5*R*)-135** was unambiguously confirmed by X-ray crystal structure analysis (Figure 3.7).

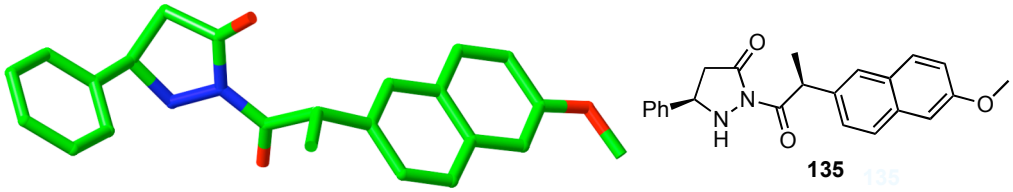


Figure 3.7: Molecular representation of the X-ray crystal structure of **135**.

3.3.3.3 Acid chloride formation

Also explored was the coupling of pyrazolidinone **83** with an appropriate acid chloride. Treatment of (*R*)-methylmandelic acid with thionyl chloride gave full conversion to the crude acid chloride **136**, by ^{1}H NMR spectroscopy (Figure 3.8). However, treatment of this compound with pyrazolidinone **83** in the presence of base gave no product after overnight reaction and returned only pyrazolidinone **83** and a number of unidentified products, apparently arising from decomposition of **136**. In order to test the stability and reactivity of the acid chloride, it was also reacted with benzylamine. This reaction gave full consumption of starting material by TLC analysis after 18 h and ^{1}H NMR spectroscopy of the crude reaction mixture confirmed complete conversion of acid chloride to amide product (the product was not isolated).

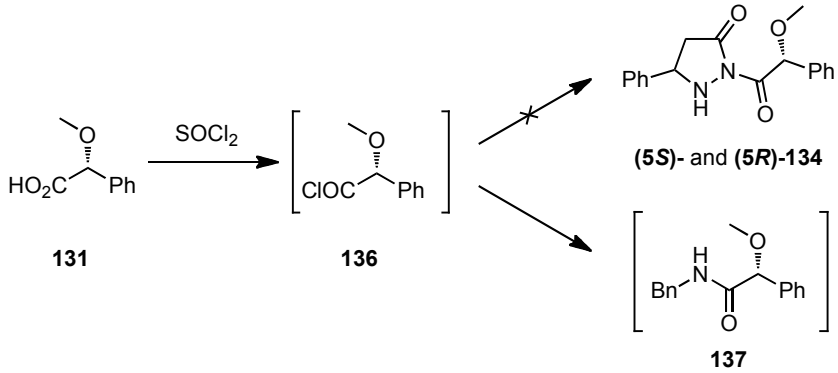


Figure 3.8: Formation of acid chloride **136** and further reaction

As an alternative, the acid chloride derived from (*S*)-Naproxen **132** was also tested. Treatment of **132** this time with oxalyl chloride gave 98 % conversion to the crude acid chloride, this time judged by HPLC analysis. However, a similar result was obtained upon treatment with **83**, although on this occasion the parent acid was returned upon work-up. This route was not pursued further.

3.3.3.4 Regioselectivity of amide coupling

The regioselectivity of the amide coupling of **83** to an acid had not as yet been unambiguously determined, although it was anticipated to proceed *via* the N(1) nitrogen to give compounds of type **A** (Figure 3.9). However, reaction at N(2) was also possible to give compounds of type **B**.

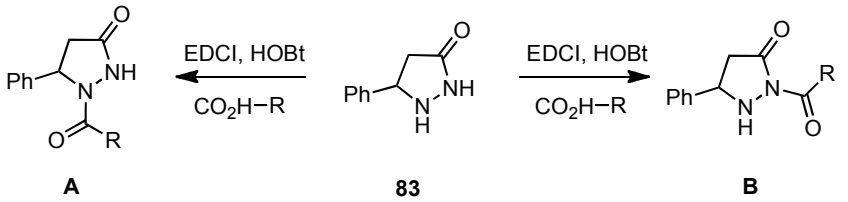


Figure 3.9: Potential regioselectivity of amide coupling of **83**

It was not possible to determine the regioselectivity of reaction from ^{1}H or ^{13}C NMR spectroscopic analysis. The X-ray crystal structure data of compound **(5*R*)-135** (see Figure 3.7) showed that the product in this case was the N(2)-acylated compound. However, the generality of the reaction had not been established. ^{15}N NMR spectroscopy had already proved an excellent method to determine the site of acylation for N(1)-protected pyrazolidinones (see Section 2.3.1). As an analysis method, it has the advantage that it can be applied to analogues for which X-ray crystal structure data could not be obtained (e.g. if said compound is not crystalline). Hence, for selected compounds the values of ^{15}N chemical shifts were obtained experimentally by $^{1}H,^{15}N$ HMBC and, in certain cases, also calculated at the B3LYP/6-31G* level of theory (Table 3.5). Compounds **85** and **114** were chosen as reference compounds for which the regiochemistry was already established (entries 1 and 2). Analysis of this data found that the chemical shift of the N(1)-nitrogen was diagnostic. For **85** (entry 1), where this nitrogen has 3 substituents and sp^2 character, the chemical shift is 127 ppm. When there are only 2 substituents and the nitrogen has sp^3 character, as with compound **114** (entry 2), the shift is significantly5 upfield at 103 ppm. The values of N(1) and N(2) are slightly lower than the calculated values, as seen previously, with an average deviation of 10.9 ppm. There is nonetheless good agreement between the experimental and theoretical data.

The chemical shift for N(1) of (*S*)-Naproxen derived diastereoisomer **(5*R*)-135** was found to be 104 ppm, consistent with the N(2)-acylation already established from X-ray crystal structure data (entry 3). To rule out the possibility that in each case the two isolated diastereoisomers were, in fact, different regioisomers, the ^{15}N chemical shifts of (*R*)-methylmandelic acid derived diastereoisomers **(5*S*)-** and **(5*R*)-134** were also obtained (entries 4 and 5). These were found to be almost identical to those of **(5*R*)-135**, confirming that these compounds had the same hybridisation at each nitrogen atom. Calculations on compound **(5*S*)-134** again showed good

agreement between the experiment and theory. Additional chemical shift values were obtained for compounds **(5*S*)-127** and **(5*S*)-133**, one diastereoisomer for each different acid coupled to pyrazolidinone **83** (entries 6 and 7). Each compound gave chemical shift values consistent with N(2)-acylation.

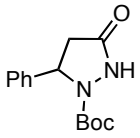
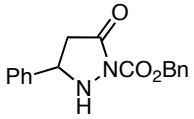
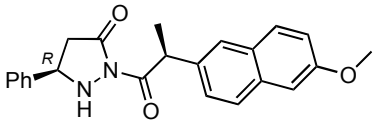
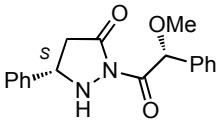
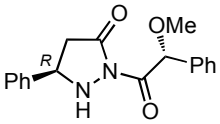
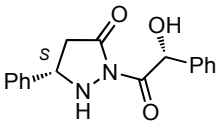
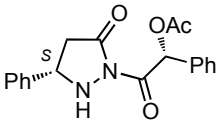
Entry	Compound	Structure	Experimental (ppm)		B3LYP/6-31G* (ppm)	
			N(1)	N(2)	N(1)	N(2)
1	**85**		127	147	139.9	147.7
2	**114**		103	167	115	185
3	**(5*R*)-135**		104	192	-	-
4	**(5*S*)-134**		104	192	115	209
5	**(5*R*)-134**		104	191	-	-
6	**(5*S*)-127**		104	189	-	-
7	**(5*S*)-133**		104	190	-	-

Table 3.5: ^{15}N NMR experimental and theoretical chemical shift data for selected diastereoisomers

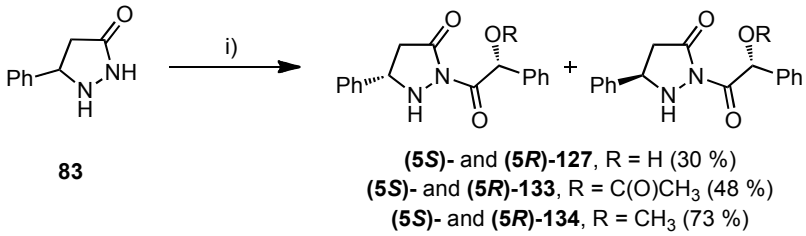
3.3.3.5 Combination

At the conclusion of optimisation studies it was found that, in order to maximise reaction yield:

- DMF was a better solvent for the reaction than THF
- pyrazolidinone **83** should be added to the other reagents after 5 minutes
- two equivalents of coupling reagents would give a small improvement
- the use of (*R*)-methylmandelic acid **131** or (*S*)-Naproxen **132** was preferable to (*R*)-mandelic acid itself.

With these conclusions in mind, a potential optimised reaction protocol was tested where two equivalents each of (*R*)-methylmandelic acid **131**, EDCI and HOBt were employed

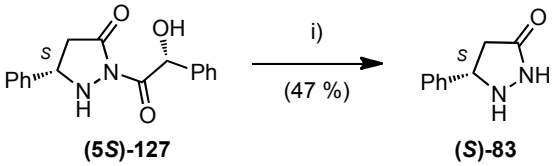
with DMF as solvent (Scheme 3.3). With this combination, the isolated yield of diastereoisomers **(5*S*)-** and **(5*R*)-134** was now 73 %. A lower 48 % product yield was observed with (*R*)-acetylmandelic acid, though this still represents an improvement over unoptimised conditions with this acid. Interestingly, when the same protocol was applied using (*R*)-mandelic acid **126** itself, the isolated yield was poor at just 30 %.



Scheme 3.3: *Reagents and conditions*: i) 2 eq EDCI, 2 eq HOBt, 2 eq (*R*)-mandelic acid **126** , (*R*)-acetylmandelic acid **130** or (*R*)-methylmandelic acid **131**, DMF, 5 min then **83**.

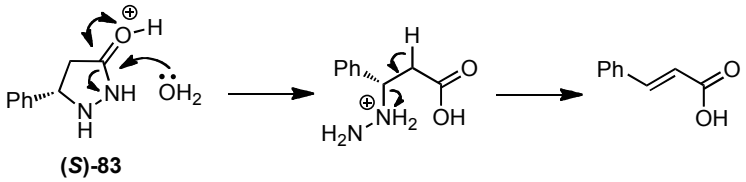
3.4 Chiral acid cleavage

With conditions for the generation and separation of diastereoisomeric amides of pyrazolidinone **83** established, it was then necessary to investigate a method for the removal of the chiral acid and so generate enantiomerically pure pyrazolidinone **83**. A survey of the available literature suggested a variety of potential conditions and a number were explored for the cleavage of (*R*)-mandelic acid **126** derived diastereoisomer **(5*S*)-127**.[32] Unsuccessful conditions included stirring with either lithium hydroxide in aqueous hydrogen peroxide,[90] potassium *tert*-butoxide in diethyl ether,[91] 15 % aqueous KOH solution[92] or refluxing with sodium nitrate in concentrated sulphuric acid.[93] Unfortunately, all these conditions gave complex mixtures of products containing neither starting material nor any pyrazolidinone **83**. On the other hand, it was found that refluxing of **(5*S*)-127** in 6 M hydrochloric acid overnight gave a 47 % yield of the pyrazolidinone **(*S*)-83**, after basic work-up (Scheme 3.4).[94]



Scheme 3.4: *Reagents and conditions*: i) 6 M hydrochloric acid, reflux, 18 h.

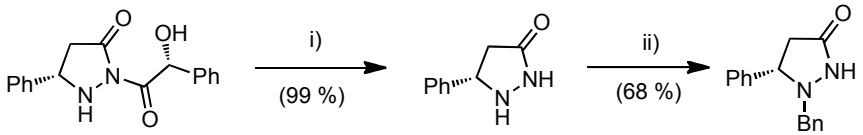
Subsequent examination of the crude reaction mixture by ^{1}H NMR spectroscopic analysis identified the major by-product as cinnamic acid (**83**: cinnamic acid 72:28). It was theorised that the cinnamic acid was the result of hydrolysis of the amide bond of **(*S*)-83**, followed by elimination of hydrazine (Figure 3.10).



(*S*)-83

Figure 3.10: Hydrolysis of **(*S*)-83** followed by elimination of hydrazine to give cinnamic acid

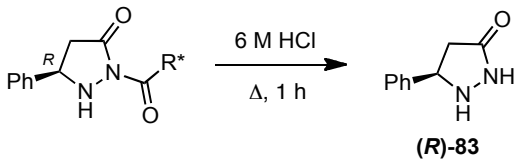
This was corroborated by exposing racemic **83** to the same strong acid conditions. After 3 h, ^{1}H NMR spectroscopy of the crude reaction mixture showed approximately 60 % conversion of **83** to cinnamic acid. In order to minimise hydrolysis, the reaction time for the amide cleavage of **(5*S*)-127** was reduced. It was found that quantitative conversion had taken place after 1 h, with the product **(*S*)-83** isolated in a much improved 95 % yield (Scheme 3.5). The absolute configuration of **(*S*)-83** was established by derivatisation to the known *N*(1)-benzyl pyrazolidinone **(*S*)-138** by condensation of **(*S*)-83** with benzaldehyde, followed by reduction with sodium borohydride to give **(*S*)-138** in 68 % yield. Chiral HPLC showed the ee was >98 % and the absolute configuration was confirmed by comparison of the specific rotation to the literature value ($[\alpha]^{20}_{D}$ –125 (*c* = 0.9, dichloromethane), literature value $[\alpha]^{20}_{D}$ –163 (*c* = 0.9, dichloromethane)).[95]



(5*S*)-127 **(*S*)-83** **(*S*)-138**

Scheme 3.5: *Reagents and conditions*: i) 6 M hydrochloric acid solution, reflux, 1 h; ii) benzaldehyde, EtOH, rt, overnight, then $NaBH_4$, rt.

Identical conditions were then applied to diastereoisomers derived from (*R*)-methylmandelic acid and (*S*)-Naproxen (Table 3.6). The cleavage of diastereoisomer **(5*R*)-134** gave a lower yield of **(*R*)-83** of 57 %, compared to the cleavage of diastereoisomer **(5*S*)-127** (entry 1). When (*S*)-Naproxen derived diastereoisomer **(5*R*)-135** was exposed to these conditions, the yield was particularly low at 18 % (entry 2). Clean product was isolated directly from the basic work-up, in this case, indicating decomposition of **(5*R*)-135** to base labile compounds.

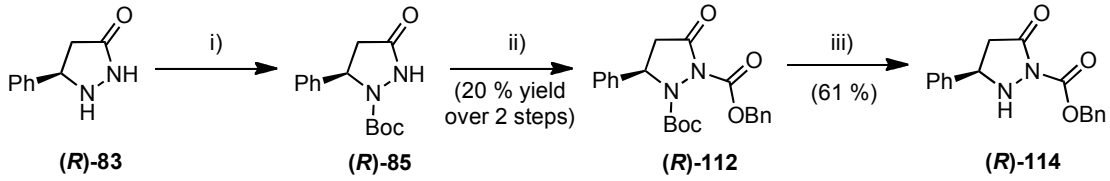


Entry	Diastereoisomer	R*	Yield (%)
1	**(5*R*)-134**	(*R*)-methylmandelic	57
2	**(5*R*)-135**	(*S*)-Naproxen	18

Table 3.6: Cleavage of diastereoisomers **(5*R*)-134** and **(5*R*)-135**

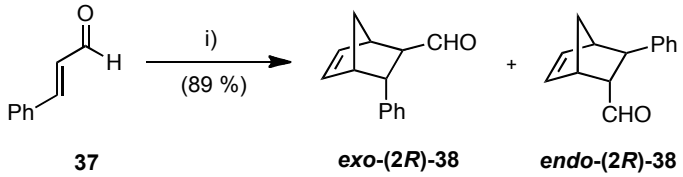
3.5 Synthesis and testing of enantioenriched catalyst (*R*)-114

As the greatest quantity of **(*R*)-83** was available at this time (1.43 g), this material was advanced to target chiral catalyst **(*R*)-114**, utilising identical chemistry to that of the achiral series (Scheme 3.6, see Section 2.4.2.3). Firstly, pyrazolidinone **(*R*)-83** was selectively Boc protected at the N(1) position to then allow carboxybenzyl functionalisation of the N(2) position to give compound **(*R*)-112** in 20 % yield from **(*R*)-83**. Boc deprotection with TFA gave catalyst **(*R*)-114** in 61 % isolated yield.



Scheme 3.6: *Reagents and conditions*: i) di-*tert* butyl dicarbonate, Na_2CO_3, dioxane-water, rt; ii) NaH, CH_2Cl_2, then benzyl chloroformate, -78 ºC to rt then toluene, reflux; iii) CF_3COOH, CH_2Cl_2, rt, then saturated $NaHCO_3$ solution, CH_2Cl_2.

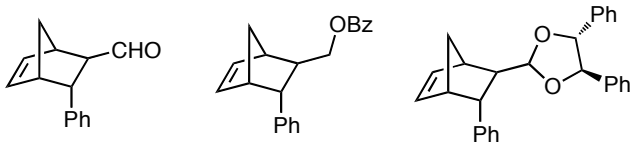
Enantioenriced catalyst **(*R*)-114** was then tested in the Diels-Alder cycloaddition of (*E*)-cinnamaldehyde **37** and cyclopentadiene and the Diels-Alder adducts ***exo*-(2*R*)-38** and ***endo*-(2*R*)-38** were isolated in 89 % yield and a 65:35 *exo*:*endo* diastereoselectivity (identical to that found with racemic catalyst **114**)(Scheme 3.7).



Scheme 3.7: *Reagents and conditions*: i) 20 mol% **(*R*)-114**, 20 mol% triflic acid, cyclopentadiene, methanol, rt.

A method for determining the enantiopurity of ***exo*-(2*R*)-38** and ***endo*-(2*R*)-38** was then investigated. There exist three major methods in the literature for the establishment of the enantiomeric excess of compounds ***exo*-(2*R*)-38** and ***endo*-(2*R*)-38**: chiral GC of the parent

aldehydes,[1] reduction to the corresponding alcohols followed by esterification and chiral HPLC[67] and derivatisation with (*R*,*R*)-hydrobenzoin to form diastereoisomeric acetals, which can then be examined by ^{1}H NMR spectroscopy[96] (Figure 3.11).



***exo*-(2*R*)-38** ***exo*-(2*R*)-139** ***exo*-(2*R*)-140**

Figure 3.11: Compound ***exo*-(2*R*)-38**, benzoylated derivative ***exo*-(2*R*)-139** and (*R*,*R*)-hydrobenzoin acetal ***exo*-(2*R*)-140**

Chiral GC of the parent aldehydes was investigated but, unfortunately, the chiral columns used by others to establish the enantiopurity of ***exo*-(2*R*)-38** and ***endo*-(2*R*)-38** were not available and experiments with similar columns were unable to yield full separation of all four stereoisomers to allow unambiguous ee determination. ***exo*-(2*R*)-38** and ***endo*-(2*R*)-38** were also derivatised to the corresponding benzoyl esters e.g. ***exo*-(1*R*)-139**. However, HPLC analysis of these compounds, using literature precedented methods, did not give full and reproducible separation in our hands. The parent aldehydes were also derivatised to the (*R*,*R*)-hydrobenzoin acetals e.g. ***exo*-(2*R*)-140**).[96] The introduction of a further stereogenic centre converts each pair of enantiomers into diastereoisomers, giving them different physical properties and allowing their relative quantities to be established by ^{1}H NMR spectroscopy. Examination of the peaks at 5.57 ppm and 5.56 ppm for ***exo*-(2*R*)-140** and 5.21 ppm and 5.17 ppm for ***endo*-(2*R*)-140** gave enantiomeric excesses of 48 % and 28 %, respectively. Repeat experiments confirmed these values.

3.6 Summary

Several methods for the resolution of *C*(5)-phenyl pyrazolidinone **38** were screened, with amide coupling to (*R*)-mandelic acid **126** and column chromatography of the resulting diastereoisomers selected for further investigation. Optimisation of the reaction identified (*R*)-methylmandelic acid **131** as the favoured acid component along with the use of coupling agents EDCI and HOBt with DMF as solvent. ^{15}N NMR spectroscopy was used to unambiguously establish that acylation was taking place on the N(2)-nitrogen. The subsequent diastereoisomeric products could be hydrolysed by treatment with refluxing 6 M hydrochloric acid for 1 h to generate enantioenriched pyrazolidinone **(*R*)-83**. This was derivatised to chiral catalyst **(*R*)-114** which was employed in the Diels-Alder reaction of (*E*)-cinnamaldehyde **37** and cyclopentadiene. The bicyclic products were produced in 89 % yield, with an *exo*:*endo* ratio of

65:35. Derivatisation to the (*R*,*R*)-hydrobenzoin acetals ascertained that the (2*R*) enantiomers had been produced in of 48 % and 28 % ee for *exo* and *endo* products, respectively.

Chapter 4: Double asymmetric induction in pyrazolidinone organocatalysis

This chapter outlines the development of a new series of diastereoisomeric asymmetric iminium ion organocatalysts. These compounds were accessed by exploiting the unexpected N(2)-regioselective amide coupling of pyrazolidinones to chiral acids as described in the previous chapter. One of each pair of these diastereoisomers was generally found to be markedly superior in terms of product ee in Diels-Alder processes, consistent with a "matched" and "mis-matched" pairing of the two stereocentres of each catalyst. A project of synthesis and screening of a range of different catalysts with variations in the acid component and C(5)-stereodirecting group was undertaken in order to maximise ee.

4.1 Diastereoisomeric pyrazolidinones as asymmetric catalysts

In the previous chapter, the regioselectivity of the coupling of pyrazolidinone **83** to a range of chiral acids was established unambiguously through a combination of X-ray crystal structure data and ^{15}N NMR spectroscopy (see Section 3.3.3.4). Diastereoisomeric resolution of these compounds was then used to obtain enantioenriched **(*R*)-83** for the synthesis of asymmetric pyrazolidinone catalyst **(*R*)-114**. However, these diastereoisomeric pyrazolidinone compounds themselves contain a secondary amine functionality, previously identified as being necessary for iminium ion formation and subsequent catalysis (Figure 4.1). Hence, we proposed these diastereoisomeric compounds would themselves act as iminium ion asymmetric catalysts of the Diels-Alder reaction. A number of features made these pyrazolidinones attractive as organocatalysts. Firstly, the coupled acid portion would serve as an electron-withdrawing group adjacent to the reactive centre, a feature previously identified to give an improved rate of product formation (see Chapter 2). Secondly, these diastereoisomeric catalysts could be accessed in just one synthetic step from the parent pyrazolidinone **83**, as opposed to five steps for a catalyst such as **(*R*)-114**. Finally, the introduction of a second stereodirecting group from the chiral acid had the potential to act in concert with the C(5)-stereodirecting group through double diastereodifferentiation to enhance the ee of the subsequent catalysis products.

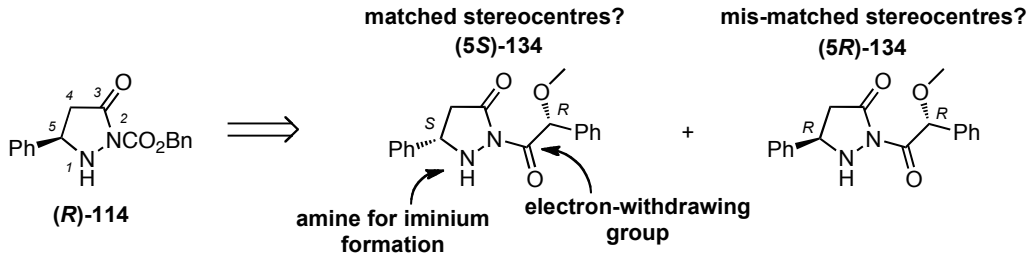
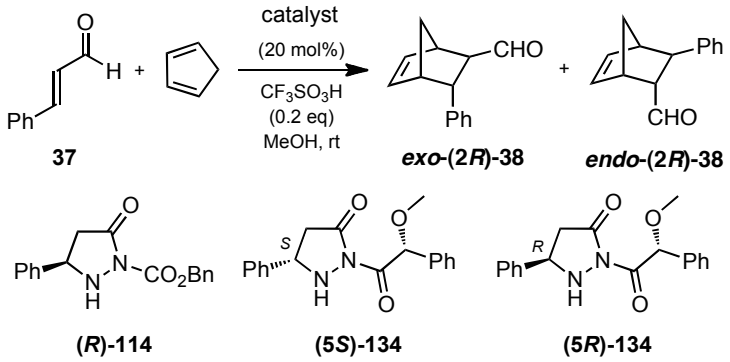


Figure 4.1: Rationale of diastereoisomer catalyst testing

4.2 Proof of principle

In order to establish that such diastereoisomeric compounds could act as catalysts in the asymmetric Diels-Alder reaction, methylmandelic acid derived diastereoisomers **(5*S*)-** and **(5*R*)-134** were chosen for proof-of-principle testing (Table 4.1). The reaction of (*E*)-cinnamaldehyde **37** and cyclopentadiene in methanol was again used as a test reaction, with triflic acid used as co-catalyst. Both diastereoisomers **(5*S*)-** and **(5*R*)-134** proved effective catalysts in terms of reaction rate, with both reactions complete by TLC within 5 hours (entries 2 and 3). However, there was a significant difference in product ee and absolute configuration. Catalyst **(5*S*)-134** gave an ee for the *exo* and *endo* diastereoisomers of 63 and 44 % ee, respectively. This was a modest improvement over catalyst **(*R*)-114** (included in entry 1) but with the opposite absolute configuration of the bicyclic products ((2*S*) as opposed to (2*R*)). This reversal between catalyst **(5*S*)-134** and **(*R*)-114** appears consistent with the absolute configuration at C(5) of each catalyst. In contrast, diastereoisomer **(5*R*)-134** gave the same (2*R*)-absolute configuration of ***exo*-** and ***endo*-38** but diminished ee's compared to **(*R*)-114** (33 and 31 % for *exo* and *endo*, respectively). These results support the theory of double diastereodifferentiation, with the stereocentres of **(5*S*)-134** acting in concert to give high ee and the stereocentres of **(5*R*)-134** acting in opposition to give low ee. Interestingly, the addition of a second stereodirecting group had no discernible effect on reaction diastereoselectivity which in all three cases was approximately 66:34 *exo*:*endo*.



Entry	Catalyst	Time (h)	Yield (%)	*exo:endo*	*exo* % ee[a]	*endo* % ee[a]
1	**(*R*)-114**	7	89	66:34	48	28
2	**(5*S*)-134**	5	77	67:33	-63	-44
3	**(5*R*)-134**	5	81	65:35	33	31

Table 4.1: Chiral catalysis results with diastereoisomeric catalysts **(5*S*)-** and **(5*R*)-134**
a) negative ee refers to (2*S*) enantiomer

4.3 Variation of acid component in diastereoisomeric catalysts

Proof of principle testing with methylmandelic acid derived compounds **(5*S*)-** and **(5*R*)-134** had shown that diastereoisomeric pyrazolidinones could act as effective iminium ion organocatalysts, with enhanced ee where the two catalysts stereocentres were 'matched' to each other. As several *C*(5)-phenyl diastereoisomeric pyrazolidinones were already in hand (synthesis described in Chapter 3), we next analysed the effect of different chiral acid groups on enantioselectivity (Figure 4.2). One further pair of diastereoisomers, maintaining *C*(5)-phenyl substitution and incorporating an *N*-carboxybenzyl-protected (Cbz) proline, were targeted to expand catalyst structural diversity. The synthesis of these two compounds and their subsequent testing alongside a range of different *C*(5)-phenyl diastereoisomeric pyrazolidinones is outlined in the following sections.

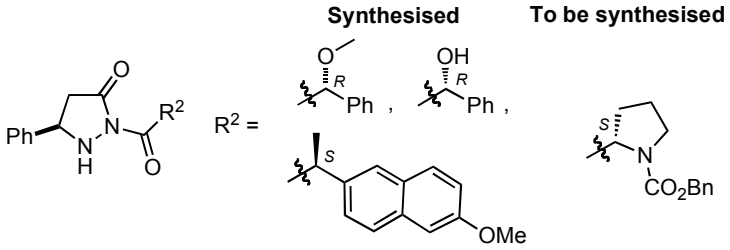
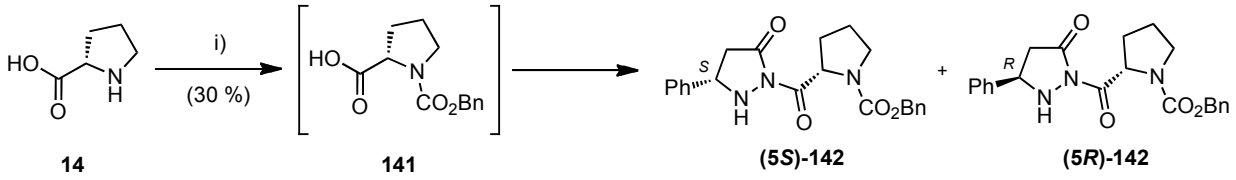


Figure 4.2: Compounds for *C*(5)-phenyl diastereoisomeric catalyst series

4.3.1 Synthesis of *N*-Cbz proline catalysts (5*S*)- and (5*R*)-142

Following the procedure of Berger *et al.*,[97] treatment of L-proline **14** with benzyl chloroformate in aqueous base gave full conversion to **141**, as judged by ^{1}H NMR spectroscopic analysis (Scheme 4.1). **141** was used directly and coupled to pyrazolidinone **83** in 30 % overall yield.

N-Cbz proline **141** and its derivatives are known to give rotamers when analysed by ^{1}H NMR spectroscopy and this appeared to be the case with diastereoisomers **(5*S*)-** and **(5*R*)-142**.[98] Variable temperature experiments with compound **(5*S*)-142** showed line-broadening at elevated temperatures, consistent with rotamers, but the coalescence temperature was too high to be reached during analysis to achieve definitive confirmation.[99]



Scheme 4.1: *Reagents and conditions*: i) benzyl chloroformate, NaOH (aq.), then EDCI, HOBt, DMF, 5 min then **83**, 18 h.

As neither **(5*S*)-** nor **(5*R*)-142** were crystalline solids, ^{15}N NMR spectroscopy was used to confirm the regioselectivity of the amide coupling. Figure 4.3 shows the experimentally and theoretically determined values for compound **(5*S*)-142**. As before, the calculated values are slightly overestimated but there is overall good agreement between the experimental and theoretical data, indicating that coupling has again taken place selectively at N(2).

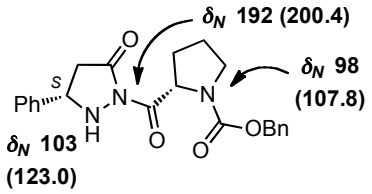
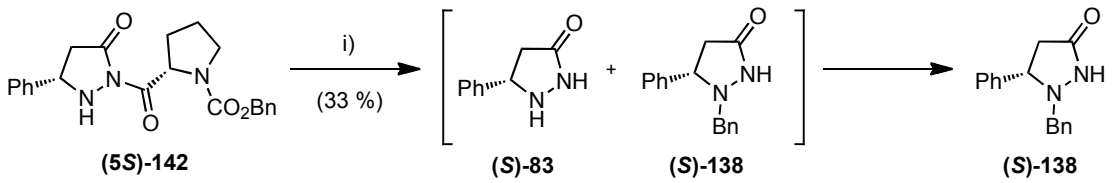


Figure 4.3: Theoretical and experimentally determined ^{15}N NMR spectroscopic data (in ppm) for **(5*S*)-142** (theoretically determined values in parenthesis)

The absolute C(5)-configuration within **(5*S*)-142** was determined by hydrolysis of the *N*-Cbz proline unit by refluxing **(5*S*)-142** in 6 M hydrochloric acid solution for 1 h (Scheme 4.2). This gave a mixture of enantioenriched pyrazolidinone **(*S*)-83** and *N*-benzyl compound **(*S*)-138** (likely arising from decomposition of the carboxybenzyl protecting group) in an 83:17 ratio, respectively.[100] This mixture of compounds was treated sequentially with benzaldehyde then sodium borohydride to give exclusively **(*S*)-138** in 33 % overall yield. The specific rotation of **(*S*)-138** $[\alpha]^{20}_{D}$ –145 (c = 0.15, CH_2Cl_2) was consistent with the (*S*)-configuration at C(5) (see Section 3.4).[95]

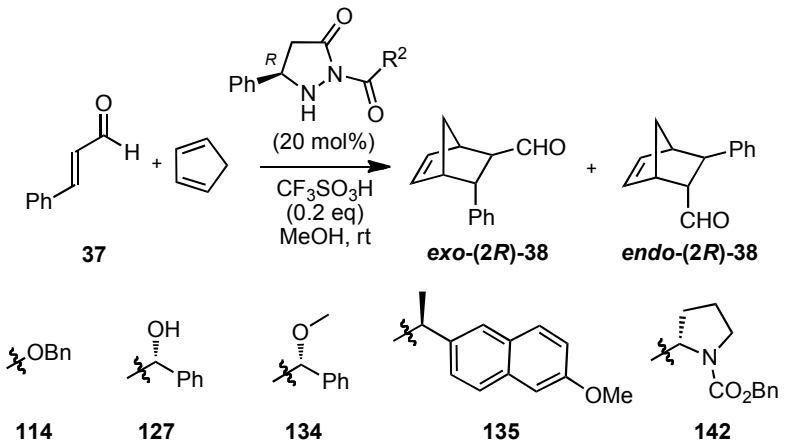


Scheme 4.2: *Reagents and conditions*: i) 6 M hydrochloric acid, reflux, 1 h, then benzaldehyde, EtOH, rt, overnight, then $NaBH_4$, rt.

4.3.2 Testing of *C*(5)-phenyl diastereoisomeric catalysts

With the desired catalysts in hand, the next stage was to evaluate these compounds in asymmetric catalysis. The analysis began by examining the influence of different chiral acid groups on enantioselectivity when an (*R*)-configuration was present at C(5) (Table 4.2). The results for catalysts **(*R*)-114** and methylmandelic acid derivative **(5*R*)-134** are also included for comparison (entries 1 and 2, respectively). All the compounds tested proved to be effective catalysts in terms of reaction rate, with the bicyclic products isolated in good to excellent yield (69-89 %) in all cases without the need for extended reaction times (5-22 h). In terms of diastereoselectivity, the catalysts were moderately *exo* selective with the exception of catalyst **(5*R*)-142** which showed no selectivity (entry 6).

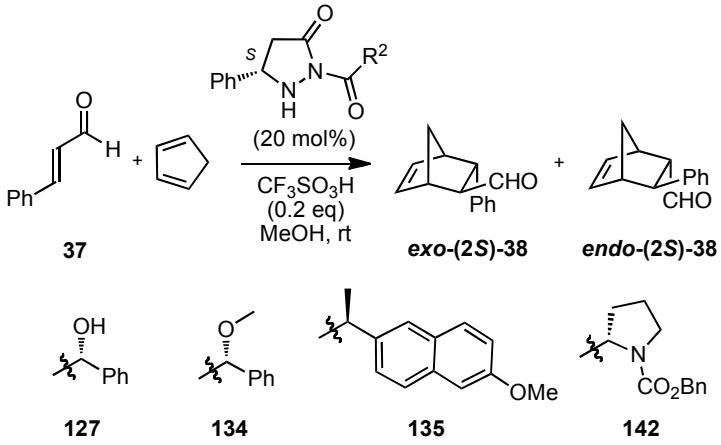
There was significantly more variation in enantioselectivity with the change in acid, although nearly all were selective for the (2*R*)-product enantiomers shown. Mandelic acid derived catalyst **(5*R*)-127** gave similar but slightly poorer ee than its methyl protected analogue (entry 3). Enantioselectivity was even lower with Naproxen derived catalyst **(5*R*)-135**, only 26 % ee for ***exo*-(2*R*)-38** and essentially racemic *endo* product (entry 5). By contrast, the highest ee's of 57 % (*exo*) and 67 % (*endo*) were observed with Cbz-proline derived **(5*R*)-142** (entries 5 and 6).



Entry	Catalyst	Time (h)	Yield (%)	*exo:endo*	*exo* % ee[a]	*endo* % ee[a]
1	**114**	7	89	66:34	48	28
2	**134**	5	81	65:35	33	31
3	**127**	6	86	62:38	28	22
4	**135**	7	69	66:34	26	<5
5	**142**	22	80	50:50	57	67

Table 4.2: Variation in enantioselectivity of (5*R*)-C(5)-phenyl pyrazolidinone with change in acid component
a) positive ee refers to (2*R*)-enantiomer

The C(5)-(*S*)-configuration diastereoisomers were next tested and the results are outlined in Table 4.3. As before, catalyst reactivity was good (reaction times 4-22 h) with a modest *exo* preference. All catalysts gave the (2*S*)-products (as shown), in contrast to the previous series. The enantioselectivities of mandelic and Naproxen derived catalysts **(5*S*)-127** and **(5*S*)-135** were superior to their respective diastereoisomers (compare entries 2 and 3 to Table 4.2). This indicates these diastereoisomers represent the stereocentre 'matched' configurations for these compounds, leading to enhanced enantioselectivity. Nonetheless, both compounds were inferior to methylmandelic acid derived catalyst **(5*S*)-134** (compare to entry 1). In contrast, Cbz-proline catalyst **(5*S*)-142** gave ee's of only 27 % (*exo*) and -18 % (*endo*) (entry 4). This represents the 'mismatched' stereocentre combination for this acid.



Entry	Catalyst	Time (h)	Yield (%)	*exo:endo*	*exo* % ee[a]	*endo* % ee[a]
1	**134**	5	77	67:33	63	44
2	**127**	6	82	62:38	54	45
3	**135**	4	71	58:42	45	52
4	**142**	22	82	56:44	27	-18

Table 4.3: Variation in enantioselectivity of (5*S*)-C(5)-phenyl pyrazolidinone with change in acid component
a) positive ee refers to (2*S*) enantiomer, negative to (2*R*)

At this stage, (*R*)-C(5)-phenyl Cbz-proline catalyst **(5*R*)-142** had been identified as the most enantioselective of those tested (Figure 4.4). We next looked to examine the influence of the C(5)-stereodirecting group in isolation from the choice of chiral acid and these investigations are described in the following sections.

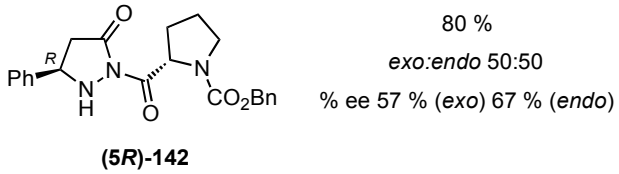


Figure 4.4: Most enantioselective catalyst screened at this stage

4.4 Variation of stereodirecting group

With the screen of different acid groups complete, we next examined the influence of the stereodirecting group at C(5). In order to study the influence of this group in isolation from other substituent effects, (*S*)-Naproxen was chosen as a standard acid component and compounds with trifluoromethyl, methyl, benzyl and *tert*-butyl functionality were targeted (Figure 4.5). Also of interest were compounds with no stereodirecting group at C(5) as these would illustrate the influence of the acid component in isolation. Two compounds, one with *gem*-dimethyl substitution at C(5) and one with no substitution at all, were chosen. It was envisaged that all compounds could be accessed from the amide coupling of (*S*)-Naproxen with the appropriate pyrazolidinone, using the standard protocol developed in Section 3.3.

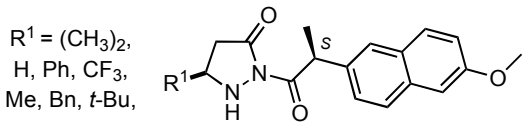
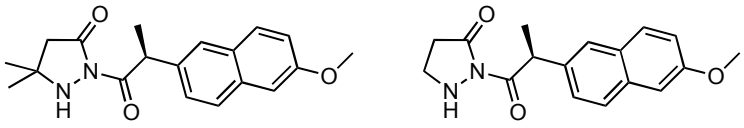


Figure 4.5: Targets for Naproxen-derived diastereoisomeric catalyst series

4.4.1 No stereodirecting group

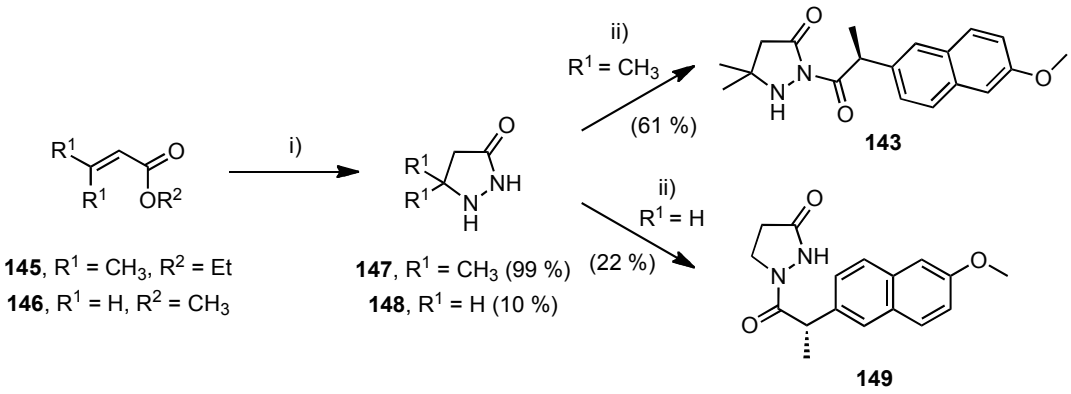
The first two catalysts targeted were *gem*-dimethyl substituted **143** and unsubstituted **144** (Figure 4.6). For these compounds, any stereoinduction would arise solely from the stereocentre derived from the chiral acid.



143 **144**

Figure 4.6: Targeted catalysts **143** and **144**

All of the catalysts in this series were envisaged to come from the amide coupling of (*S*)-Naproxen **132** with the appropriate pyrazolidinone, itself arising from condensation of hydrazine with an α,β-unsaturated ester. In the case of catalysts **143** and **144**, the parent pyrazolidinones were derived from methyl 3-methyl-2-butenoate **145** and methyl acrylate **146**, respectively (Scheme 4.3). While *C*(5)-*gem*-dimethyl pyrazolidinone **147** was isolated in near quantitative yield, the yield of unsubstituted pyrazolidinone **148** was disappointing at only 10 %. White *et al.* have reported a very similar synthesis of **148** (using ethyl acrylate as starting material) and the yield in that case was also low (24 %).[75] Nonetheless, the reaction gave sufficient material for the next step. The coupling of *gem*-dimethyl pyrazolidinone **147** proceeded well and gave catalyst **143** in 61 % yield, with the expected regiochemistry of **143** confirmed by ^{15}N NMR spectroscopy and by obtaining the crystal structure (Figure 4.7). In contrast, the coupling of pyrazolidinone **148** gave a significantly lower yield of product which was identified as the N(1)-acylated compound **149**.



Scheme 4.3: *Reagents and conditions*: i) hydrazine hydrate, EtOH, reflux then toluene, reflux (**148** only); ii) (*S*)-Naproxen **132**, EDCI, HOBt, DMF, 5 min then **147** or **148**, 18 h.

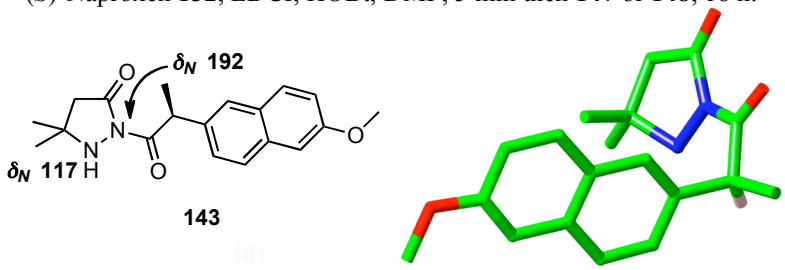


Figure 4.7: Analysis of compound **143**- experimentally determined ^{15}N NMR spectroscopic data (in ppm) and molecular representation of the X-ray crystal structure.

Evidence for the N(1)-acylation of **149** came from a number of sources. Firstly, the compound had very poor solubility in relatively non-polar organic solvents, such as dichloromethane. Good solubility could only be achieved in polar solvents such as acetonitrile and DMSO. **149** was rotameric in the solution phase and this was confirmed by variable temperature ^{1}H NMR spectroscopic analysis in CD_3CN.[99] In contrast, other Naproxen derived compounds in this series had not shown any hindered rotation in the solution phase. ^{15}N NMR spectroscopic analysis gave a single resonance at 141 ppm and it was not possible from the ^{1}H,^{15}N HMBC spectra to unambiguously assign this chemical shift to either nitrogen atom. Theoretical calculations indicated that N(2)-acylated **144** would have ^{15}N chemical shifts of 104.0 and 207.5 ppm, both of which markedly differ from the single experimentally determined resonance (Figure 4.8a)). Calculations on N(1)-functionalised compound **149** gave chemical shifts for N(1) and N(2) of 147.9 ppm and 150.5 ppm (Figure 4.8b)). Taking into account the margin of error seen with ^{15}N NMR spectroscopy on related compounds (see Sections 2.3.1 and 3.3.3.4), either of these values would be consistent with the experimentally determined shift of 141 ppm. Finally and most compellingly, an X-ray crystal structure of **149** was obtained that indicated N(1)-acylation.

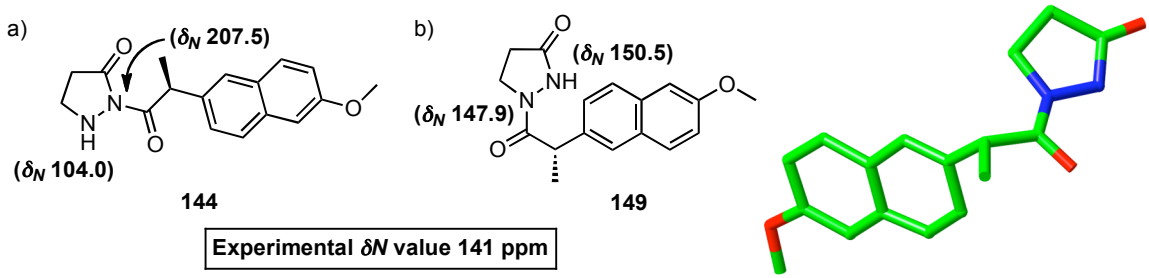


Figure 4.8: Theoretically determined ^{15}N NMR spectroscopic data (in ppm, values in parenthesis) for a) potential regioisomer **144**; b) **149** and the molecular representation of the X-ray crystal structure of **149**

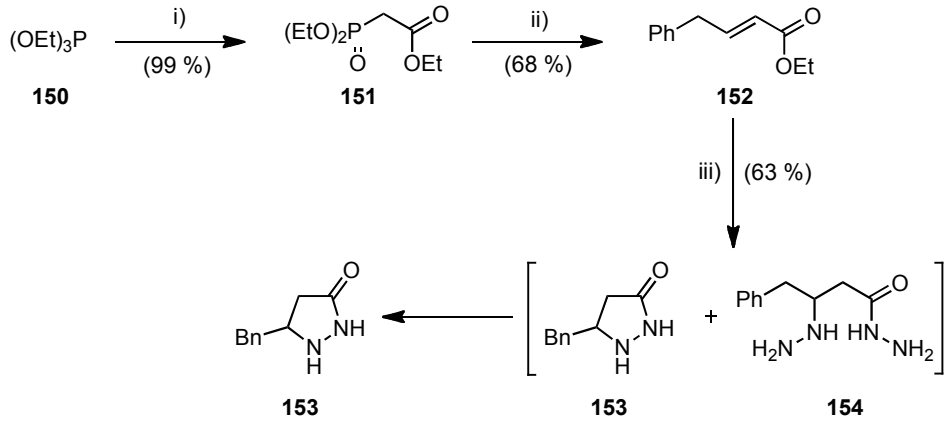
Despite this unexpected result, compound **149** was still of interest as an iminium ion catalyst as it contains a di-substituted nitrogen atom at N(2) which could (though unlikely) be utilised for iminium ion formation and subsequent catalysis. As this nitrogen atom was part of an amide, it would have lower nucleophilicity in comparison to a secondary amine and so the rate of iminium ion formation was likely to be slow. Nonetheless, we felt the result would be of value and compounds **144** and **149** were both taken forward for testing.

4.4.2 Naproxen derived diastereoisomeric catalysts

The next stage was the synthesis of a series of diastereoisomeric compounds with (*S*)-Naproxen as a common chiral acid group at N(2) and different substituents at the C(5)-position. *C*(5)-trifluoromethyl, methyl, benzyl and *tert*-butyl derivatives were targeted.

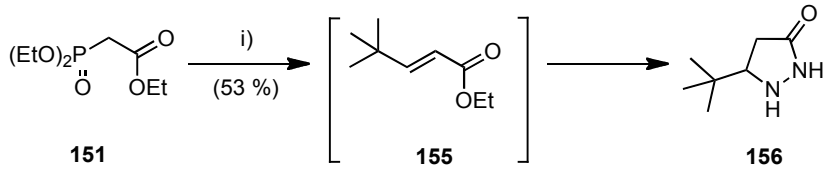
The synthesis of precursors *C*(5)-methyl pyrazolidinone **71** and *C*(5)-trifluoromethyl pyrazolidinone **84** have already been described (see Section 2.1 and 2.2.2, respectively) and so the first pyrazolidinone targeted was *C*(5)-benzyl **153** (Scheme 4.4). In this case, the necessary α,β-unsaturated ester **152** was not commercially available and had to be synthesised from phenylacetaldehyde and phosphonate ester **151**, making use of a modified Horner-Wadsworth-Emmons reaction using methylmagnesium bromide as base, as developed by Davies and co-workers.[101]

Phosphonate ester **151** was first synthesised in 99 % yield by refluxing triethyl phosphite **150** in ethyl bromoacetate, followed by treatment of **151** with phenylacetaldehyde to give ester **152** in 68 % yield (Scheme 4.4). In analogy to *C*(5)-phenyl pyrazolidinone **83**, refluxing of **152** with three equivalents of hydrazine hydrate in ethanol gave a 75:25 mixture of **153** and a compound believed to be **154**, respectively. **154** was never isolated and the structure has not been unambiguously confirmed. However, refluxing the above mixture in toluene gave only pyrazolidinone **153**, which was isolated in 63 % yield.



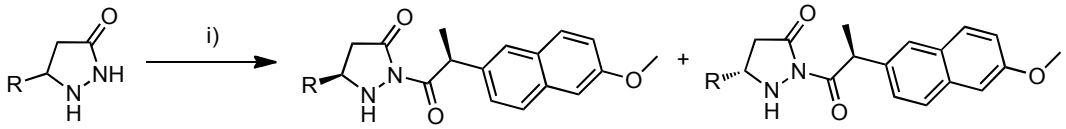
Scheme 4.4: *Reagents and conditions*: i) ethyl bromoacetate, reflux; ii) methylmagnesium bromide, THF, 0 ºC to rt then phenylacetaldehyde, reflux; ii) 3 eq hydrazine hydrate, ethanol, reflux then toluene, reflux.

C(5)-*tert*-Butyl pyrazolidinone **156** was accessed *via* a similar route, using the Horner-Wadsworth-Emmons reaction of phosphonate ester **151** and pivalaldehyde to give α,β-unsaturated ester **155** as exclusively the (*E*)-isomer by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Scheme 4.5). Without purification, **155** was treated with hydrazine and refluxed in ethanol to give **156** in 53 % yield from **151**.



Scheme 4.5: *Reagents and conditions*: i) pivalaldehyde, *n*-butyllithium, THF, -78 ºC to rt, then hydrazine hydrate, EtOH, reflux.

With the necessary pyrazolidinones in hand, their coupling to (*S*)-Naproxen **132** was explored (Scheme 4.6). Yields were modest (15-40 %) but gave acceptable quantities of crude material and so no attempt was made to optimise procedures further. Separation of the diastereoisomers was generally challenging but achieved with a combination of column chromatography and/ or recrystallisation.



71 R = CH_3
84 R = CF_3
153 R = Bn
156 R = *t*-Bu

(5*S*)- and **(5*R*)-157**, R = CH_3 (26 %)
(5*R*)- and **(5*S*)-158**, R = CF_3 (15 %)
(5*S*)- and **(5*R*)-159**, R = Bn (27 %)
(5*R*)- and **(5*S*)-160**, R = *t*-Bu (40 %)

Scheme 4.6: *Reagents and conditions*: i) (*S*)-Naproxen **132**, EDCI, HOBt, DMF, 5 min then **71**, **84**, **153** or **156**, 18 h.

The isolated diastereoisomers were normally solids amenable to the growing of single crystals for X-ray crystallographic analysis. X-ray crystal structures of each of the two diastereoisomers of the *C*(5)-trifluoromethyl (**(5*S*)-** and **(5*R*)-158**) and *C*(5)-benzyl (**(5*R*)-** and **(5*S*)-159**) compounds were obtained, allowing their absolute configurations to be unambiguously identified (Figures 4.9 and 4.10, respectively). X-ray crystal structure data could not be obtained for either of C(5)-*tert*-butyl catalysts **(5*S*)-** and **(5*R*)-160**. The absolute configurations of these compounds was initially assigned by their R_f values (in comparison to other compounds in the series) and later by comparison of results in catalysis.

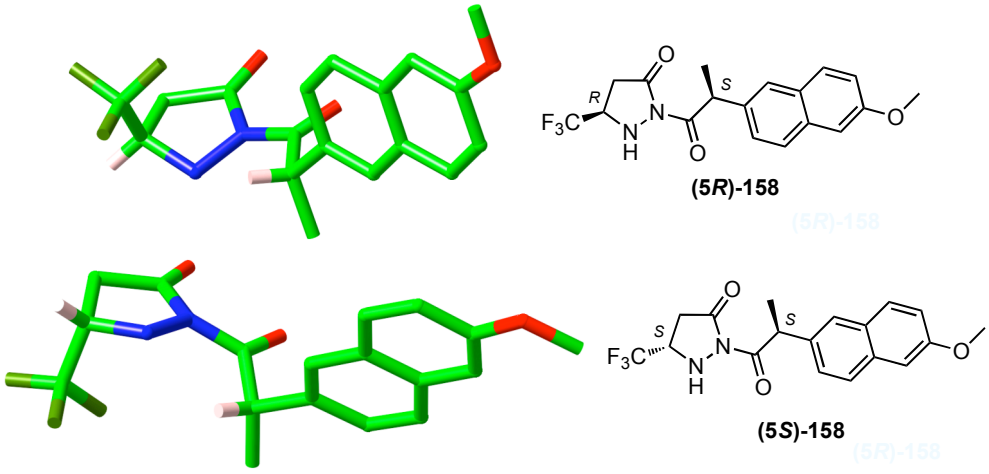


Figure 4.9: Molecular representation of the X-ray crystal structures of **(5*R*)-** and **(5*S*)-158**

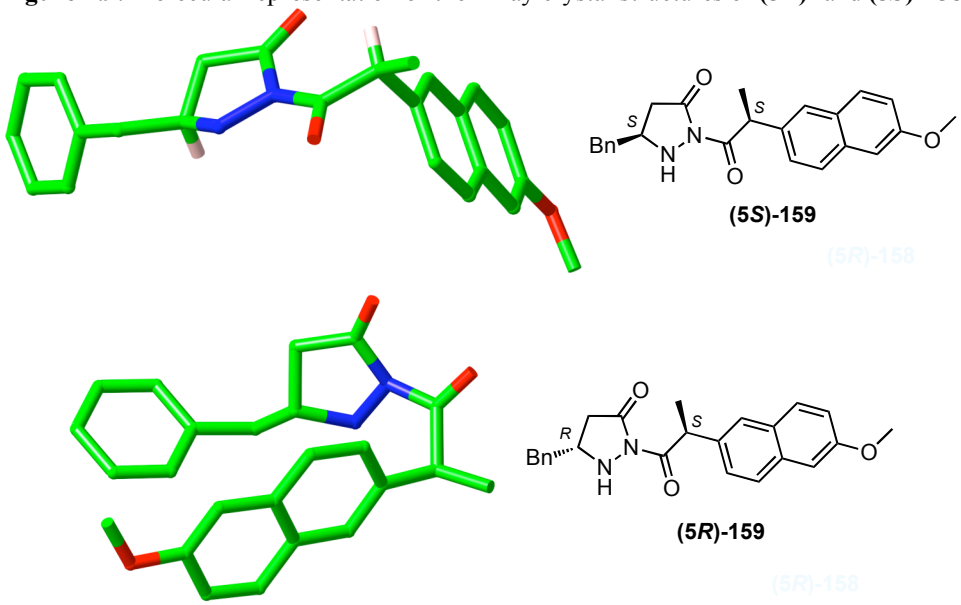


Figure 4.10: Molecular representation of the X-ray crystal structures of **(5*S*)-** and **(5*R*)-159**

Despite repeated attempts, it was not possible to obtain a clean sample of *C*(5)-methyl diastereoisomer **(5*R*)-157**. The best that could be achieved was a 26:74 ((5*S*):(5*R*)) mixture of the two compounds arising from careful column chromatography in a diethyl ether/ petrol

system. Repeated chromatography or recrystallisation could not improve on this ratio. Formation of the hydrochloride salt of this diastereoisomeric mixture and subsequent recrystallisation was also attempted but, again, the same ratio was obtained. Hence, only diastereoisomer **(5*S*)-157** was taken on for catalyst testing. An X-ray crystal structure of **(5*S*)-157** was obtained and this confirmed the assigned (*S*)-C(5)-stereoconfiguration (Figure 4.11).

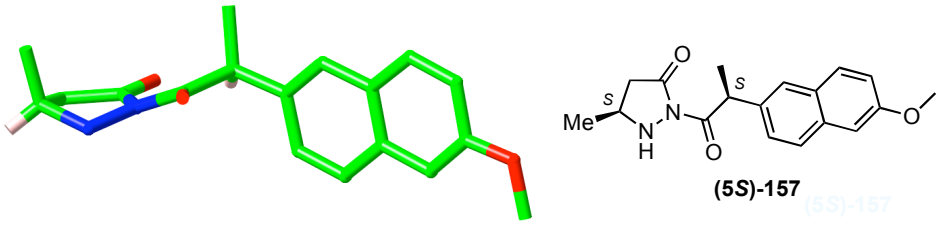


Figure 4.11: Molecular representation of the X-ray crystal structure of **(5*S*)-157**

4.4.3 Testing of *N*(2)-(*S*)-Naproxen diastereoisomeric catalysts

The testing of the Naproxen derived catalysts began by examining the extent of stereoinduction by the acid component in isolation using *gem*-dimethyl catalyst **143** (Figure 4.12). Diels-Alder products were produced with very modest selectivity for the (2*S*)-enantiomers of 13 % (*exo*) and 27 % (*endo*), meaning the catalyst is significantly less enantioselective than 'matched' catalyst **(5*S*)-135** and consistent with the C(5) stereodirecting group being required for good enantioselectivity (see Table 4.3). However, the enantioselectivity is generally superior to that of 'mis-matched' catalyst **(5*R*)-135**, indicating the importance of the relative configuration of the two catalyst stereocentres (see Table 4.2).

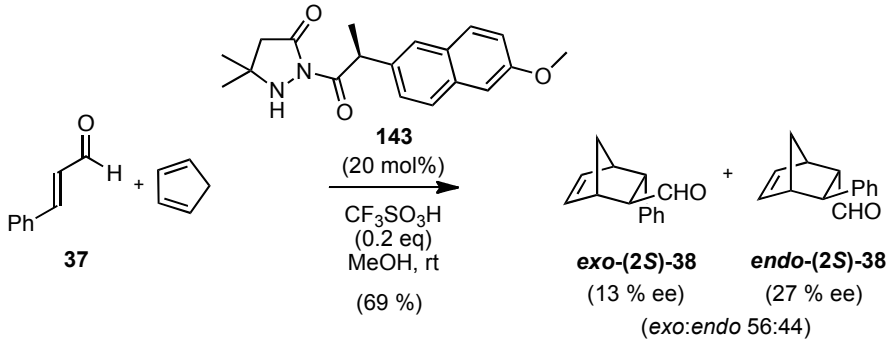
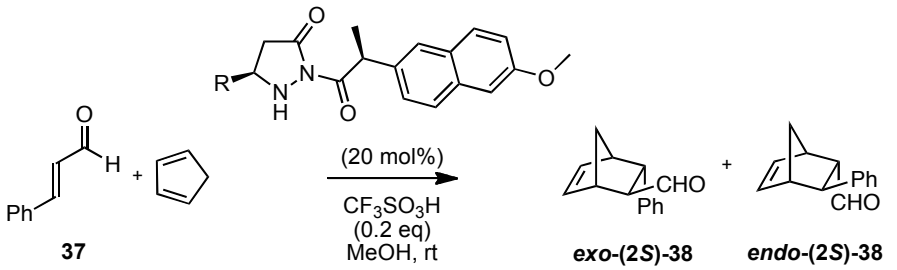


Figure 4.12: Testing of *gem*-dimethyl catalyst **143**

We next examined the effect on enantioselectivity of different C(5) substituents and their absolute configuration. The first set of compounds tested possessed an 'up' configuration at C(5), as drawn in Table 4.4 (this represents (5*R*)-configuration for phenyl, *tert*-butyl and trifluoromethyl substitution, (5*S*)-configuration for benzyl and methyl substitution). The

previously reported result with phenyl substituted catalyst **(5*R*)-135** is included for reference (entry 1). Efficient catalysis was observed in all cases along with general *exo* diastereoselectivity. However, enantioselectivity was generally poor, the best being benzyl catalyst **(5*S*)-159** (entry 4). These results are consistent with the trend observed with phenyl catalysts **(5*S*)-** and **(5*R*)-135** that the 'up' configuration at C(5) is mis-matched to the stereocentre present in Naproxen, leading to low ee's in catalysis.

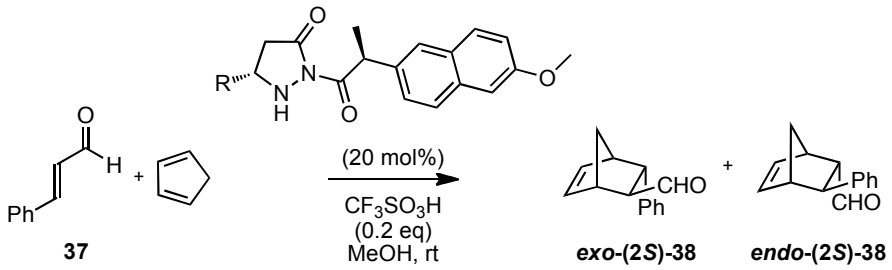


37 ***exo*-(2*S*)-38** ***endo*-(2*S*)-38**

Entry	R	Catalyst	Yield (%)	*exo:endo*	*exo* % ee[a]	*endo* % ee[a]
1	Ph	**(5*R*)-135**	69	66:34	-26	<5
2	Me	**(5*S*)-157**	73	64:36	-9	20
3	CF_3	**(5*R*)-158**	88	51:49	3	32
4	Bn	**(5*S*)-159**	82	63:37	33	44
5	*t*-Bu	**(5*R*)-160**	93	59:41	13	30

Table 4.4: Variation in enantioselectivity with change in "mis-matched" stereodirecting group at C(5) (stereodirecting group all 'up' as drawn)
a) positive ee refers to (2*S*) enantiomer, negative to (2*R*)

The results with the corresponding 'down' configuration at C(5) are outlined in Table 4.5. In all cases, this diastereoisomer was superior to its pair in terms of enantioselectivity, consistent with this combination of stereocentres being 'matched' for high enantioselectivity. The highest overall enantioselectivity was achieved when a trifluoromethyl group was present with *exo* and *endo* diastereoisomers produced in 61 % and 71 % ee, respectively (entry 2). Interestingly, incorporation of a benzyl stereodirecting group, in analogy to the imidazolidinone catalysts of the MacMillan group (entry 3),[1] gave no selectivity benefit compared to a phenyl substituent (entry 1). Similarly, the sterically bulky *tert*-butyl group gave no improvement in the enantioselectivity in comparison to phenyl (32 % *exo*, 40 % *endo*, entry 4)). Unfortunately, it was not possible to isolate the analogous *C*(5)-methyl derivative for testing. Again, diastereoselectivity was generally similar across the series with a small *exo* preference for all but trifluoromethyl catalyst **(5*S*)-158** which showed the greatest *endo* preference (46:54 *exo*:*endo*, entry 5).

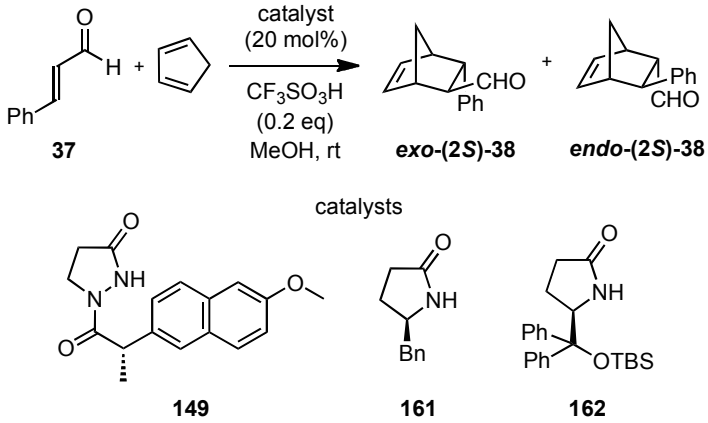


Entry	R	Catalyst	Yield (%)	*exo:endo*	*exo* % ee[a]	*endo* % ee[a]
1	Ph	**(5*S*)-135**	71	58:42	45	52
2	CF_3	**(5*S*)-158**	79	46:54	61	71
3	Bn	**(5*R*)-159**	95	58:42	39	49
4	*t*-Bu	**(5*S*)-160**	74	53:47	42	40

Table 4.5: Variation in enantioselectivity with change in "matched" stereodirecting group at C(5) (stereodirecting group all 'down' as drawn)
a) positive ee refers to (2*S*) enantiomer, negative to (2*R*)

4.4.4 Amides as iminium ion organocatalysts

The amide coupling of unsubstituted pyrazolidinone **148** with (*S*)-Naproxen had given rise to N(1)-acylated compound **149**. As a secondary amide rather than a secondary amine, compound **149** was tested to ascertain whether the nitrogen at N(2) was sufficiently nucleophilic to act as an iminium ion catalyst in Diels-Alder reactions (Table 4.6). In addition, two other chiral secondary amides, **161** and **162**, were tested. These compounds represent intermediates in the synthesis of chiral carbene catalysts used within the group and were readily available in the lab.[102] Catalyst **149** gave an isolated product yield of 88 % after 24 h reaction but low ee (21 % *exo* and 10 % *endo*, entry 1). In contrast, compounds **161** and **162** required 48 h reaction to give reasonable yields of racemic products (entries 2 and 3). The high *endo* diastereoselectivity (14:86 *exo*:*endo* in both cases) and extended reaction times indicate that the products are likely arising from the background reaction catalysed by the triflic acid co-catalyst ($t^{1/2}$ 10 h, *exo*:*endo* 14:86, see Section 2.4.1). This implies that essentially no iminium ion formation is taking place with these compounds and the background reaction is responsible for all turnover observed. With compound **149**, the low but non-zero enantioselectivity implies some meaningful interaction between the catalyst and substrate in which stereochemical information is being transmitted. This may be *via* the formation of an iminium ion, however the low nucleophilicity of the amide centre makes this less likely. Another possibility is that **149** is acting as a hydrogen-bonding (Brønsted base) catalyst and activating *trans*-cinnamaldehyde by protonation. The mechanism of action of catalyst **149** has not been unambiguously determined and requires further investigation.

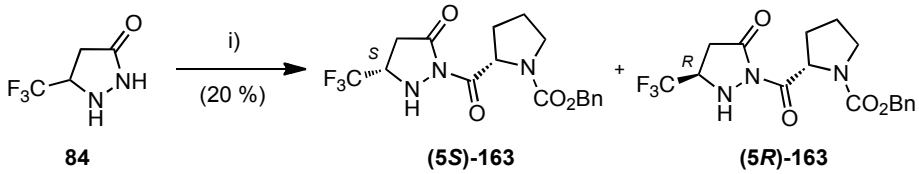


Entry	Catalyst	Time (h)	Yield (%)	*exo:endo*	*exo* % ee[a]	*endo* % ee[a]
1	**149**	24	88	33:67	21	10
2	**161**	48	71	15:85	0	0
3	**162**	48	69	15:85	0	0

Table 4.6: Catalysis with a small number of chiral amides
a) positive ee refers to (2*S*) enantiomer

4.5 Combination

In terms of enantioselectivity, trifluoromethyl had been identified as the best C(5)-stereodirecting group and the carboxybenzyl-protected proline as the best acid component. Hence, a combined catalyst was targeted in the hope of maximising the enantioselectivity of the catalyst. The amide coupling of pyrazolidinone **84** to *N*-Cbz-proline **141** proceeded in low but acceptable yield to give diastereoisomeric compounds **(5*S*)-** and **(5*R*)-163** (Scheme 4.7). Analysis of compound **(5*R*)-163** included variable temperature ^{1}H NMR spectroscopy (both diastereoisomers were rotameric in the solution phase)[99] and ^{15}N NMR spectroscopy to confirm the expected substitution pattern (Figure 4.13).



Scheme 4.7: *Reagents and conditions*: i) (*S*)-*N*-(benzyloxycarbonyl)-proline **141**, EDCI, HOBt, DMF, 5 min then **84**, 18 h.

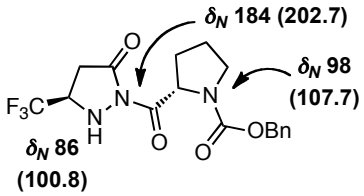
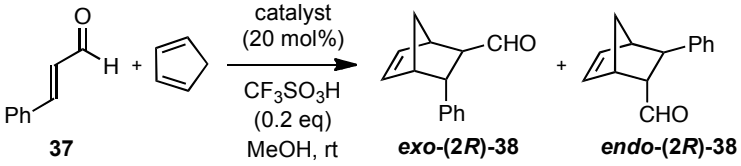
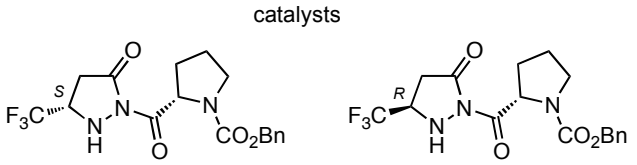


Figure 4.13: Theoretical and experimentally determined ^{15}N NMR spectroscopic data (in ppm) for **(5*R*)-163** (theoretically determined values in parenthesis)

Both diastereoisomers were tested but "matched" catalyst **(5*R*)-163** proved the more enantioselective of the two compounds giving the (2*R*)-products in 65 % (*exo*) and 75 % (*endo*) ee (Table 4.7). This represents the highest enantioselectivities observed in this series. In addition, the catalyst proved to be significantly *endo* diastereoselective in a ratio of 35:65, which is highly unusual in the organocatalysed Diels-Alder reaction when cyclopentadiene is used as the diene component.





Entry	Catalyst	Yield (%)	*exo:endo*	*exo* % ee[a]	*endo* % ee[a]
1	**(5*S*)-163**	78	47:53	-30	7
2	**(5*R*)-163**	84	35:65	65	75

Table 4.7: Chiral catalysis results with diastereoisomeric catalysts **(5*S*)-** and **(5*R*)-163**
a) positive ee refers to (2*R*) enantiomer, negative to (2*S*)

4.6 Summary

A new series of asymmetric iminium ion organocatalysts utilising diastereoisomeric pyrazolidinones were investigated. In order to explore the influence of the acid component on enantioselectivity, *C*(5)-phenyl pyrazolidinone **83** was coupled to *N*-Cbz proline **141** as an alternative series to the *C*(5)-phenyl catalysts previously synthesised. (*S*)-Naproxen **132** was used as a standard acid component to allow the effect of varying the *C*(5)-stereodirecting group on the pyrazolidinone ring to be investigated. A series of diastereoisomeric compounds varying in this substituent were synthesised from direct coupling of the appropriate pyrazolidinone to (*S*)-Naproxen **132**. Also synthesised was a *C*(5)-*gem*-dimethyl derivative **143** to act as a reference. In catalysis, the combination of the two stereocentres was shown to have either an enhancing or diminishing effect in comparison to either stereocentre in isolation, depending on their relative configurations. Higher ee's were observed when the two stereocentres were 'matched' to each other and lower ee's when they were 'mis-matched'. *C*(5)-Trifluoromethyl, Cbz-proline catalyst **(5*R*)-163** was identified as being the most enantioselective and also displayed an unusually high *endo* diastereoselectivity of 35:65 *exo*:*endo*.

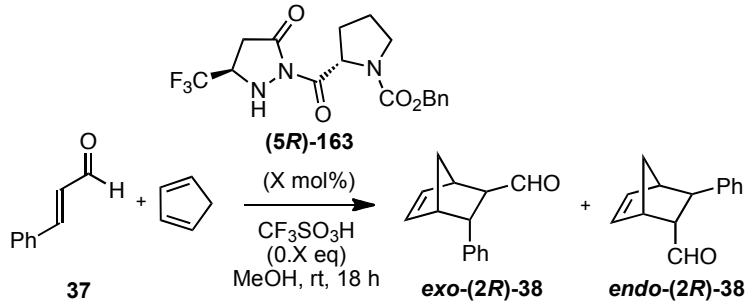
Chapter 5: Asymmetric catalysis with optimised catalyst (5*R*)-163 and investigations into active catalytic species

This chapter describes optimisation of asymmetric catalysis using C(5)-trifluoromethyl, Cbz-proline catalyst **(5*R*)-163**. The catalyst was then screened against a range of aldehydes with the (2*R*)-enantiomer of the products favoured. In order to rationalise this finding, an iminium ion derived from racemic catalyst **114** was isolated and characterised. This compound was found to have (*Z*)-geometry in the key N=C bond but also to have undergone ring-opening due to acid catalysed methanolysis of the pyrazolidinone ring. This led us to isolate a chiral acyclic hydrazide, derived from optimised asymmetric catalyst **(5*R*)-163**, which has now been identified as a highly active and enantioselective catalyst of the Diels-Alder reaction. This compound likely represents the key active catalytic species in reactions employing **(5*R*)-163**.

5.1 Application of optimised catalyst (5*R*)-163

5.1.1 Optimisation of reaction conditions

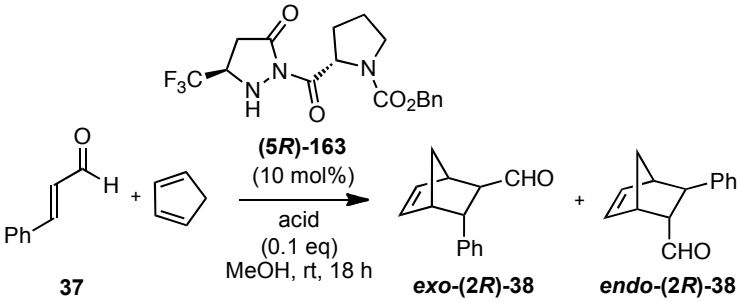
With evaluation of the catalyst structure completed, the next stage was optimisation of the reaction conditions. This first factor examined was catalyst loading (Table 5.1). In all cases, the catalyst concentration was maintained at 0.19 M. Dropping the catalyst loading to 10 mol% had no effect on yield or enantioselectivity (entry 2). A small drop in enantioselectivity was observed when loading was taken down to 5 mol% (entry 3). Therefore, it was decided to maintain catalyst loading at 10 mol%. The ratio of *exo* and *endo* diastereoisomers was identical in all cases (35:65 *exo*:*endo*).



Entry	Loading (mol%)	Yield (%)	*exo* % ee	*endo* % ee
1	20	84	65	75
2	10	85	65	73
3	5	85	62	69

Table 5.1: Variation of catalyst loading of catalyst **(5*R*)-163**

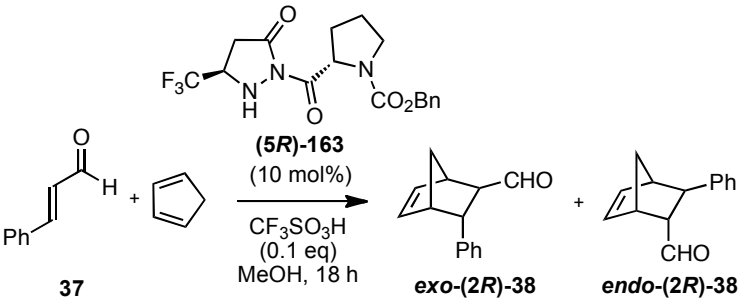
A small screen of alternative acid co-catalysts to triflic acid was next undertaken, using 10 mol% catalyst loading (Table 5.2). Both hydrochloric and perchloric acid gave very similar results as co-catalysts to triflic acid (entries 2 and 3). In contrast, trifluoroacetic acid showed only 50 % conversion after extended (48 h) reaction, resulting in an isolated yield of 47 % (entry 4). Enantioselectivity was also lower. With these results, it was decided to continue with triflic acid as co-catalyst. Again, a diastereoisomeric ratio of 35:65 *exo*:*endo* was found for all examples.



Entry	Acid	Yield (%)	*exo* % ee	*endo* % ee
1	CF_3SO_3H	85	65	73
2	HCl	87	64	75
3	$HClO_4$	83	67	68
4[a]	TFA	47	60	70

Table 5.2: Variation of acid co-catalyst
a) Reaction time 48 h

The final factor examined was reaction temperature (Table 5.3). Lowering the temperature to 5 ºC maintained good reactivity and very slightly improved the ee of the *endo* diastereoisomer to 78 % (entry 2). Further reduction to -10 ºC improved the enantioselectivity further to 73 % (*exo*) and 82 % (*endo*) (entry 3). However, the yield was slightly reduced to 75 %. It was decided to keep reaction temperature at 5 ºC as a compromise between good yield and enantioselectivity. Once again, diastereoselectivity was unchanged at 35:65 *exo*:*endo* in all cases.



Entry	Temp	Yield (%)	*exo* % ee	*endo* % ee
1	RT	85	65	73
2	5	90	65	78
3	–10	75	73	82

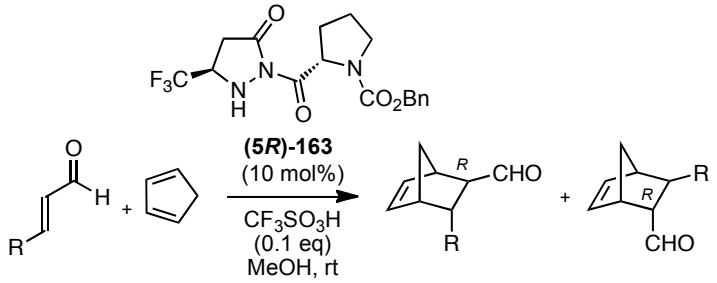
Table 5.3: Optimisation of reaction temperature

5.1.2 Substrate screen

With the optimisation of reaction conditions complete, it was now possible to assess the substrate scope of the Diels-Alder reaction catalysed by **(5*R*)-163**. Reaction optimisation with (*E*)-cinnamaldehyde **37** had indicated that reactions should be run at 5 ºC with 10 mol% catalyst loading and using triflic acid as a co-catalyst. Unfortunately, lowering the temperature with many analogues adversely effected reaction rate and this was attributed to the low solubility of many of the analogues in methanol at lower temperatures. Hence, reactions were carried at room temperature except where aldehyde solubility allowed a lower temperature to be used.

The results of the aldehyde screen are outlined in Table 5.4.[103] In all cases, the ee's of the major *endo* diastereoisomer were superior to the *exo*, although both followed the same trends. Yields were generally good, ranging from 70-86 %. Testing showed that catalysis was compatible with aldehydes with a range of electronic properties. The electron-donating 4-methoxy and electron-withdrawing 4-chloro and 4-nitro substituents were all well tolerated, giving *endo* ee's of 77 %, 82 % and 77 %, respectively.

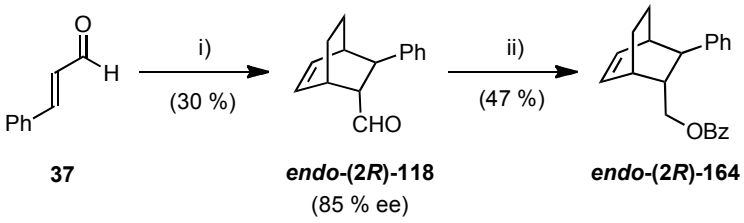
Different substitution patterns were also well tolerated. 2-Nitrocinnamaldehyde, for example, gave 84 % ee for the *endo* product, the best result obtained in the series (entry 5). Bulky naphthyl substituents also gave good results, with 2-naphthyl and 1-naphthyl substituents giving *endo* ee's of 79 % and 73 % ee, respectively (entries 6 and 7). However, alkyl substituents were less well tolerated with both *n*-propyl and ethyl ester substituents giving significantly lower ee's than the other derivatives explored (entries 8 and 9). Diastereoselectivity was approximately 35:65 *exo*:*endo* for the majority of derivatives tested. An exception was aldehydes with substituents in the 2-position, namely 2-nitrocinnamaldehyde (entry 5) and the 1-napthyl aldehyde (entry 7), which gave appreciably higher *endo* diastereoselectivity (an average of 18:82 *exo*:*endo* for the two compounds). It should also be noted that the (2*R*)-enantiomer was preferred for all derivatives and diastereoisomers.



Entry	R	Yield (%)	*exo:endo*	*exo* % ee	*endo* % ee
1	Ph	84	35:65	65	73
2[a]	4-OMe-C_6H_4	85	35:65	72	77
3[a]	4-Cl-C_6H_4	86	34:66	68	82
4	4-NO_2-C_6H_4	85	36:64	59	77
5	2-NO_2-C_6H_4	85	17:83	65	84
6	2-Nap	88	38:62	62	79
7	1-Nap	83	19:81	61	73
8[a]	Pr	76	35:65	30	46
9	CO_2Et	70	47:53	3	10

Table 5.4: Substrate tolerance of catalyst **(5*R*)-163** in Diels-Alder reactions
a) Reactions at 5 ºC

During substrate screening with racemic catalyst **114**, attempts to expand reaction scope to other dienes, other than cyclopentadiene, had proved fruitless (see Section 2.5.2). A single reaction, using (*E*)-cinnamaldehyde **37** and cyclohexadiene with catalyst **(5*R*)-163** was explored (Scheme 5.1). It should be noted that this reaction cannot be realised with MacMillan's first or second generation imidazolidinone catalysts.[42,85] Reaction was very sluggish, with no discernible product formation by TLC analysis after 18 h. When the reaction time was extended to 6 days, some product formation was observed with 30 % conversion of the aldehyde to a 5:95 *exo*:*endo* mixture of diastereoisomeric products by ^{1}H NMR spectroscopic analysis. In this case, separation of the two diastereoisomers was possible and only the *endo* diastereoisomer ***endo*-(2*R*)-118** was isolated in 30 % yield. Derivatisation to benzoyl ester ***endo*-(2*R*)-164** allowed the ee of 85 % to be determined.[104] The specific rotation of ***endo*-(2*R*)-118** was determined to be -35.7, confirming the absolute configuration to be (1*S*,2*R*,3*R*,4*R*) by comparison to the literature value of +82 ((1*R*,2*S*,3*S*,4*S*) enantiomer, >95 % ee, *c* 1.0, dichloromethane).[85] To our knowledge, this represents the first time ***endo*-118** has been synthesised using organocatalytic methods.



37 ***endo*-(2*R*)-118** (85 % ee) ***endo*-(2*R*)-164**

Scheme 5.1: *Reagents and conditions*: i) 10 mol% **(5*R*)-163**, 10 mol% triflic acid, cyclohexadiene, methanol, rt, 6 days; ii) sodium borohydride, methanol, rt then benzoyl chloride, triethylamine, DMAP, dichloromethane, rt.

5.2 Initial mechanistic investigations

Catalyst **(5*R*)-163** had been identified as an enantioselective catalyst of the Diels-Alder cycloaddition and screened against a range of aldehydes. The resulting adducts possessed, in all cases, (2*R*)-absolute configuration and this gives an insight into the mechanism of action. Initial catalyst design had proposed a transoid iminium ion with (*E*)-geometry for the key C=N bond (**A** in Figure 5.1) rather than (*Z*)-geometry (**B**) or either of cisoid conformations **C** and **D**.

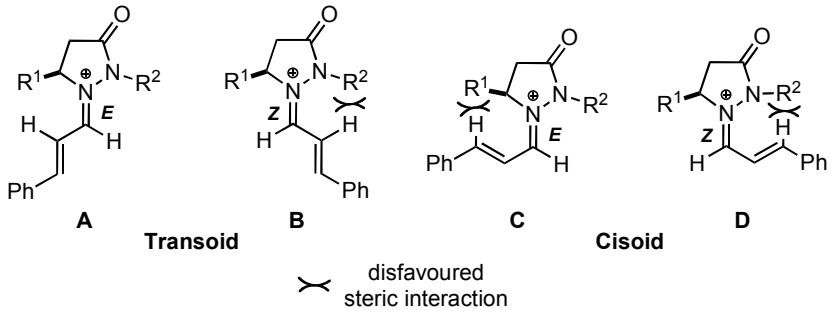


Figure 5.1: Proposed pyrazolidinone derived iminium ions

If such a model were applied to asymmetric catalyst **(5*R*)-163**, products with a (2*S*)-configuration would be expected, assuming the diene approaches anti to the trifluoromethyl stereodirecting group (Figure 5.2i)). This is not observed experimentally, with the observed (2*R*)- product configuration consistent with either a (*Z*)-configuration in this bond (Figure 5.2ii)) or the transoid conformation shown in Figure 5.2iii) (*exo* approach of the diene would also give rise to the (2*R*)-configuration observed in the *exo* product).

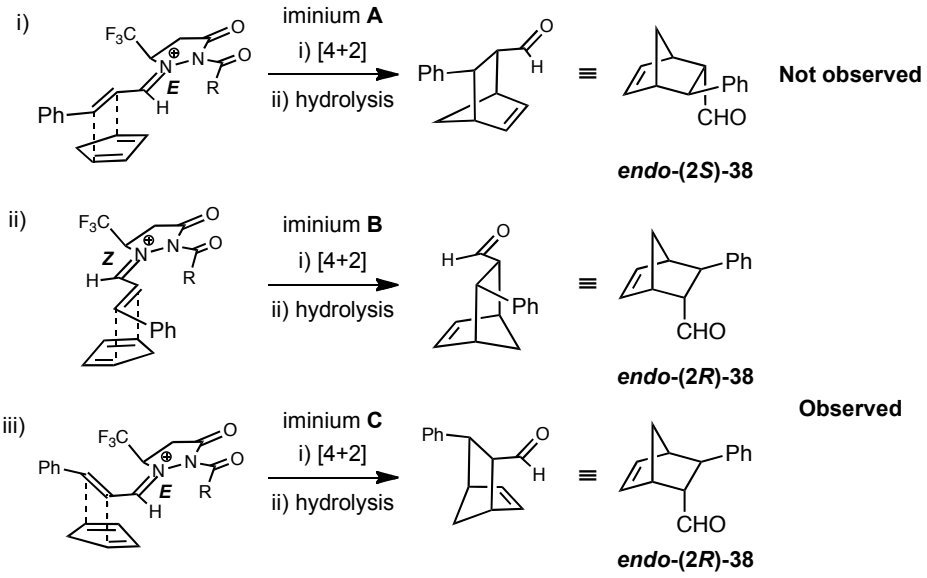
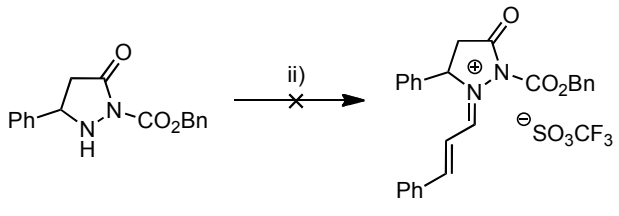


Figure 5.2: *endo* approach of cyclopentadiene to iminium ion of catalyst **(5*R*)-163** a) transoid with (*E*)-geometry; ii) transoid with (*Z*)-geometry; iii) cisoid with (*E*)-geometry

In order to ascertain which of these models best represented the active catalyst species, we attempted to isolate an iminium ion from an appropriate catalyst. The isolation and characterisation of one such compound is outlined in the following section.

5.2.1 Isolation of iminium ion on model system

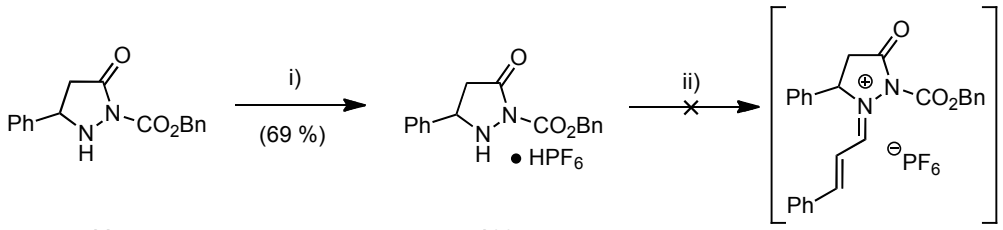
We began with model studies on racemic pyrazolidinone **114** (Scheme 5.2). Initial attempts to prepare and isolate an iminium ion followed the method of Mayr *et al.* with **114** and freshly distilled (*E*)-cinnamaldehyde **37** taken up in a bi-phasic mixture of ethyl acetate and a 0.17 M aqueous solution of triflic acid.[105] ^{1}H NMR spectroscopic analysis of the crude reaction mixture after 24 h showed no reaction had taken place and a 1:1 mixture of **114** and (*E*)-cinnamaldehyde **37** was returned. The reaction was repeated using THF as solvent but gave the same result after 24 h reaction.



Scheme 5.2: *Reagents and conditions*: i) 0.17 M triflic acid (aq.), (*E*)-cinnamaldehyde **37**, ethyl acetate or THF, 24 h.

In order to improve reactivity, conditions that resembled those used in catalysis were examined. Following the method of Tomkinson and co-workers, the hexafluorophosphoric acid salt **166** was isolated by treatment of **114** with hexafluorophosphoric acid in ethyl acetate, then taken up

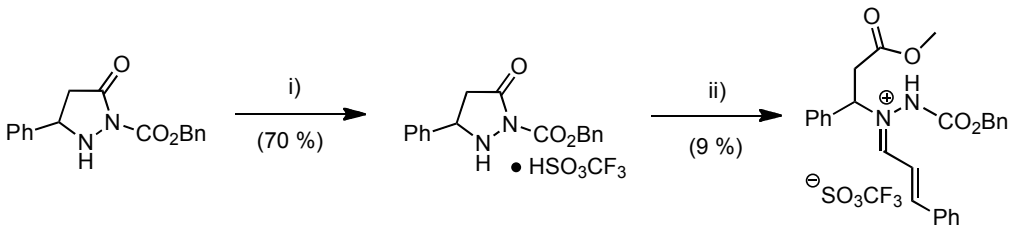
in dry methanol and (*E*)-cinnamaldehyde **37** added (Scheme 5.3).[52] After 3 days, ^{1}H NMR spectroscopy of a reaction sample indicated approximately 67 % conversion of (*E*)-cinnamaldehyde to a species with peaks consistent with **167**. However, attempted isolation of **167** by crystallisation from a hot solution of diethyl ether and dichloromethane led to decomposition to a complex mixture of products. The same reaction using ethanol as solvent (in analogy to the work of Seebach and co-workers) was also investigated but reactivity was poor and a complex mixture of products resulted when reaction time was extended (2 weeks).[38]



114 **166** **167**

Scheme 5.3: *Reagents and conditions*: i) hexafluorophosphoric acid (~65 wt. % in water), ethyl acetate; ii) (*E*)-cinnamaldehyde **37**, methanol, 3 days.

The same method was also applied to triflate salt **168**. This was isolated from **114** in 70 % yield then suspended with (*E*)-cinnamaldehyde in methanol (Scheme 5.4). Conversion to the iminium was again sluggish; after 3 days ^{1}H NMR spectroscopic analysis of a reaction sample indicated only 57 % conversion of (*E*)-cinnamaldehyde to a compound with selected peaks consistent with an iminium ion. Upon extended reaction time (3 weeks), ^{1}H NMR spectroscopic analysis of this crude mixture indicated a complex mixture of products that included a compound consistent with an iminium ion. Trituration of this mixture in diethyl ether and the minimum of dichloromethane yielded 10 mg of a yellow solid identified as the ring-opened iminium ion **169**. Repeating this process on the filtrate gave a further 3 mg of **169**, giving a 9 % yield from triflate salt **168**.



114 **168** **169**

Scheme 5.4: *Reagents and conditions*: i) triflic acid, dichloromethane; ii) (*E*)-cinnamaldehyde **37**, methanol, 3 weeks.

Low and high-resolution mass spectrometry confirmed a methoxy group had been incorporated into the expected iminium ion structure and single crystal X-ray crystallographic analysis was used to confirm the structure in the solid phase, including the configuration of the C=N and

C=C double bonds ((*Z*)- and (*E*)-configuration, respectively) and the expected transoid conformation of these bonds (Figure 5.3).

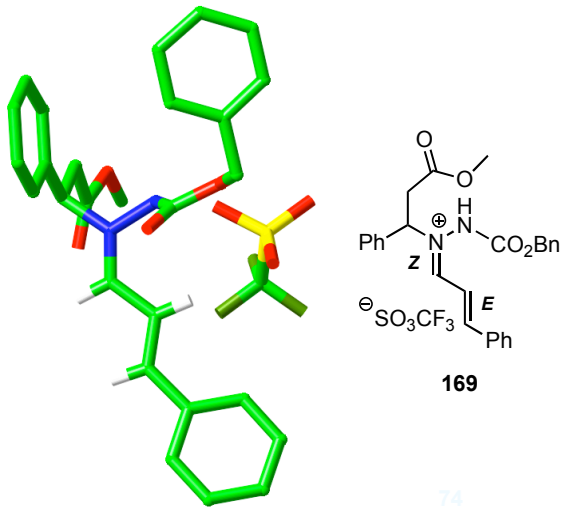


Figure 5.3: Molecular representation of the X-ray crystal structure of **169**

Control of the configuration and conformation of these bonds is crucial to achieve high asymmetric control in enantioselective reactions.[1] nOe spectroscopy was used to confirm the solution phase molecule was consistent with that observed in the solid state (Figure 5.4). The correlation of H^B to the *ortho*-aromatic proton (blue arrow) on irradiation indicated the C=C double bond had the expected (*E*)-configuration. Irradiation of the H^A proton (red arrows) showed correlation to H^C which is also consistent with the (*E*)-configuration of this bond. In addition, this correlation is consistent with the expected transoid conformation. Finally, the correlation of H^A to the side chain C*H*Ph proton indicated the (*Z*)-configuration of the N=C bond.

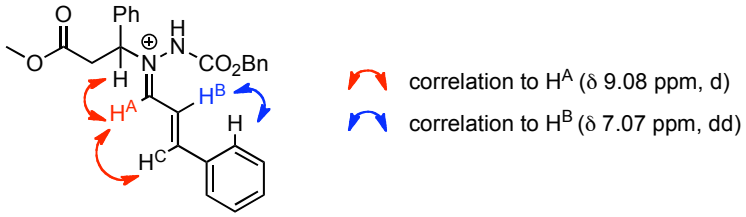


Figure 5.4: Representation of through space correlations as determined by nOe spectroscopy

In conclusion, a number of conditions for the isolation of an iminium ion derived from racemic catalyst **114** were explored, with treatment of the triflate salt **168** with (*E*)-cinnamaldehyde **37** in methanol over an extended reaction time proving fruitful. The isolated compound **169** was found to possess a (*Z*)-configuration in the key N=C double bond and a transoid conformation. Significantly, the structure of **169** indicated that methanolysis of the pyrazolidinone ring had also taken place during the reaction. The implications of this finding to the mechanism of action

of the pyrazolidinone catalyst series and, in particular, asymmetric catalyst **(5*R*)-163**, are explored in the following sections.

5.2.2 Analysis of ring-opening of chiral catalyst (5*R*)-163

The isolation of iminium **169** under conditions similar to those used in catalysis raised the question of whether a similar ring-opening process was taking place during catalytic reactions and, if so, were any newly formed compounds also catalytically active? We set out to investigate this possibility with asymmetric catalyst **(5*R*)-163** (Figure 5.5). As **(5*R*)-163** contains an imido group, rather than the amidocarbamate functionality present in racemic catalyst **114**, it was envisaged that methanolysis would take place in both an endo- (Step A) and exocyclic (Step C) manner. Step A resembles the methanolysis observed with racemic catalyst **114** to give the acyclic hydrazide **170**. **170** also contains an amide bond which might be susceptible to further attack by methanol, as shown in Step B. This would give rise to CBz-proline methyl ester **171** and hydrazide **(*R*)-172**. Steps C and D represent the reverse of this process, wherein the exocyclic methanolysis takes place first to generate **(*R*)-84** which would then be opened to hydrazide **(*R*)-172** after a second methanol attack.

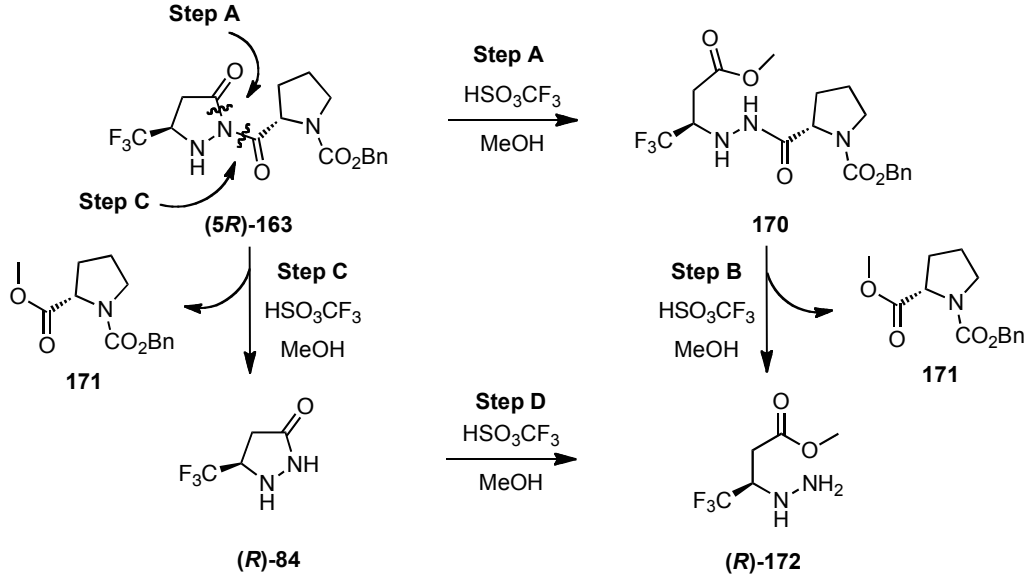
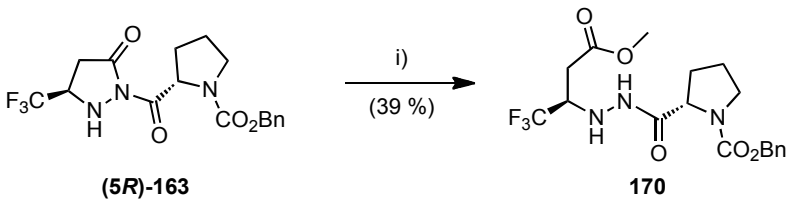


Figure 5.5: Potential methanolysis pathways of chiral catalyst **(5R)-163**

Treatment of **(5*R*)-163** with triflic acid in methanol overnight led to full consumption of starting material and the isolation of ring-opened compound **170** in 39 % yield (Scheme 5.5). Compound **170** was analysed by both ^{15}N NMR spectroscopy and by single crystal X-ray crystallography (Figure 5.6).



Scheme 5.5: *Reagents and conditions*: i) triflic acid, methanol.

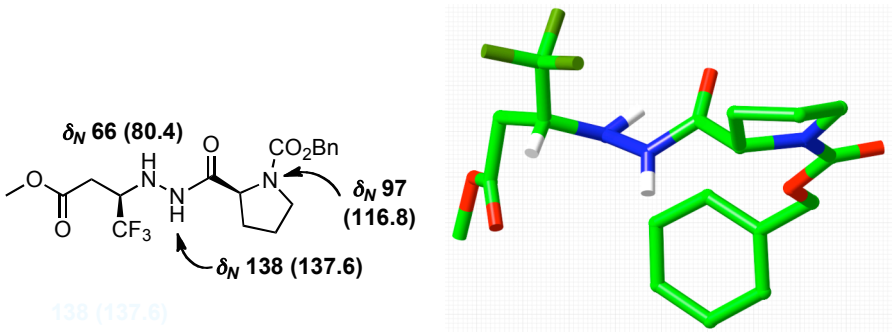
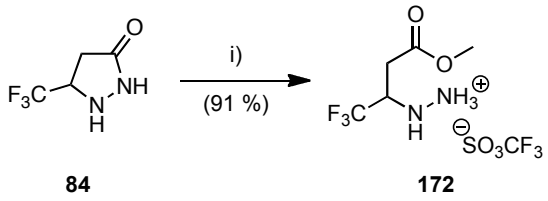


Figure 5.6: Theoretical and experimentally determined ^{15}N NMR spectroscopic data (in ppm) for **170** (theoretically determined values in parenthesis) and molecular representation of its X-ray crystal structure

It was also attempted to isolate enantioenriched **(*R*)-172** from the same reaction but the compound had high solubility in aqueous media and could not be retrieved after basic work-up. However, when racemic pyrazolidinone **84** alone was treated overnight with triflic acid in methanol, the triflate salt of **172** was readily isolated in high yield (Scheme 5.6).



Scheme 5.6: *Reagents and conditions*: i) triflic acid, methanol.

In order to determine the rate of formation of these species, the methanolysis of **(5*R*)-163** was carried out in deuterated methanol in an NMR tube. Reaction was carried out at 19 mM, identical concentration to that used with **(5*R*)-163** at 10 mol% catalyst loading. It was found that the relative concentrations of all the above compounds could be readily monitored by ^{19}F NMR spectroscopy (apart from CBz-proline methyl ester **d_3-171**). A typical NMR spectra from the experiment is shown in Figure 5.7.

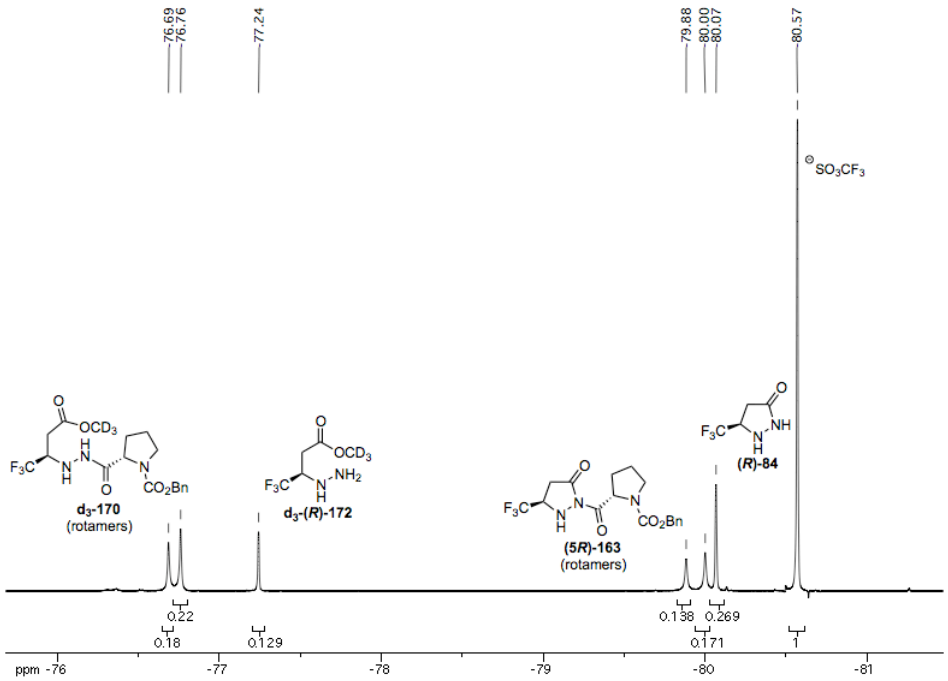


Figure 5.7: Typical ^{19}F NMR spectra from methanolysis of **(5*R*)-163** studies

The relative concentrations of fluorinated compounds **(5*R*)-163**, **d$_3$-170**, **(*R*)-84** and **d$_3$-(*R*)-172** were monitored over the course of 18 h and the results are represented graphically in Figure 5.8.[106] The relative concentration of CBz-proline methyl ester **171** was not monitored and was not included in the composition values. The graph shows that the catalyst **(5*R*)-163** is consumed steadily, with relative composition dropping to less than 5 % after 7 h (orange line). The concentration of ring-opened compound **d$_3$-170** concordantly increases to 50 % after 6 h then remains essentially constant over the rest of the reaction (red line), consistent with very slow methanolysis of **d$_3$-170** to **d$_3$-(*R*)-172** (Step B). In a separate experiment, when only **170** was exposed to triflic acid and methanol, less than 5 % methanolysis of **170** was observed after 30 h.

The exocyclic cleavage of **(5*R*)-163**, as outlined in Step C, is also observed *via* the increased concentration of **(*R*)-84** during the early part of the reaction (blue line). The concentration of **(*R*)-84** peaks at 24 % after approximately 2.5 h then declines steadily to 3 % after 18 h. This is due to the subsequent conversion of **(*R*)-84** to ring-opened compound **d$_3$-(*R*)-172** (as in Step D). As **d$_3$-(*R*)-172** forms from **(*R*)-84**, the concentration of **d$_3$-(*R*)-172** is initially low but accelerates markedly as the concentration of its precursor increases (green line). After 18 h, there has been essentially full conversion of catalyst **(5*R*)-163** to a mixture principally composed of ring-opened compounds **d$_3$-170** and **d$_3$-(*R*)-172** (50:47:3 **d$_3$-170**: **d$_3$-(*R*)-172**:**(*R*)-84**).

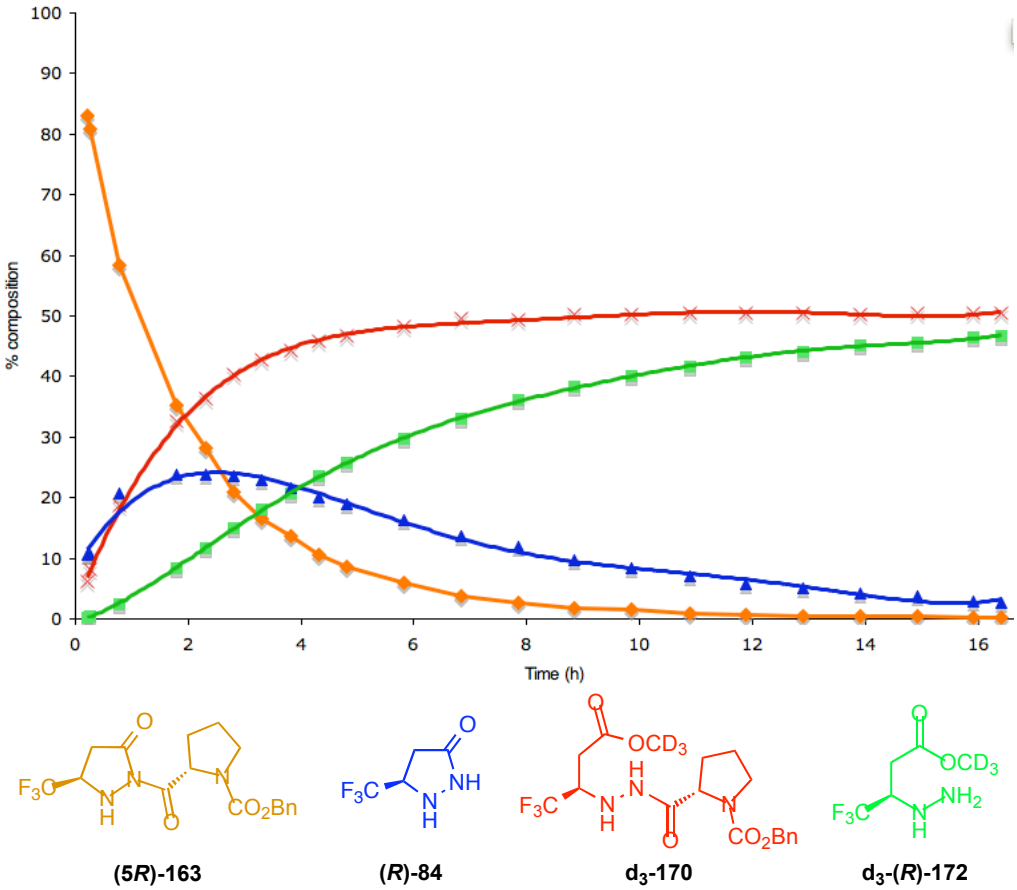


Figure 5.8: Triflic acid catalysed methanolysis of **(5*R*)-163** as monitored by ^{1}H NMR spectroscopy

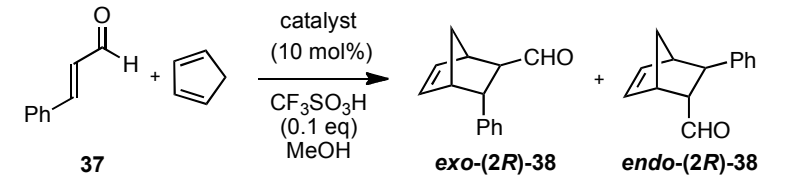
5.2.3 Application of 170 to catalysis

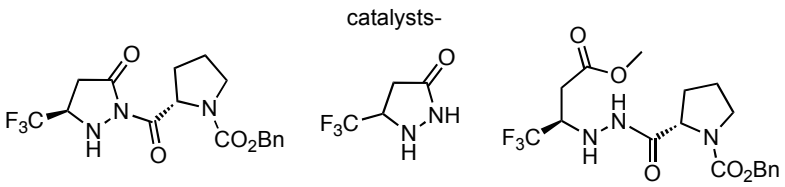
We had found that several new species were being derived from catalyst **(5*R*)-163** under conditions very similar to those used during catalysis. The next stage was to evaluate whether these compounds were themselves catalytically active and so were responsible for the observed turnover. This was obviously complicated by the fact that these compounds were known to interconvert under the reaction conditions. The exception was ring-opened hydrazide **170** which was straightforward to isolate and found to be resistant to further methanolysis. Hence, the reactivity and enantioselectivity of this component could be unambiguously determined. Unfortunately, it was not possible to isolate authentic samples of either enantioenriched **(*R*)-172** or **(*R*)-84**. Instead, racemic **84** was examined with the knowledge that interconversion to racemic **172** would take place under the reaction conditions. Hence, the use of racemic **84** served as a partial measure of both compounds activity as catalysts.

Reactions with **170** and racemic **84** were run, each with 10 mol% loading at a catalyst concentration of 19 mM and monitored by TLC (Table 5.5). The reaction with **(5*R*)-163** is included for comparison (entry 1, full consumption of (*E*)-cinnamaldehyde observed within

4 h). Isolated **170** proved to be an effective catalyst with complete reaction also observed within 4 h (entry 3). In contrast, the reaction with racemic **84** had not reached completion after 24 h, with ^{1}H NMR spectroscopic analysis indicating 82 % conversion in that time (entry 2). This implies that **84** and its ring-opened analogue are much less active than the other potential catalytic species present in the reaction. Hence, these compounds were not investigated further.

In terms of enantioselectivity, isolated catalyst **170** gave a small improvement in the enantioselectivity of ***endo*-(2*R*)-38** over the use of **(5*R*)-163** (entry 3). The high reactivity of **170** led us to investigate lowering catalyst loadings. Pleasingly, the use of just 1 mol% of **170** showed complete reaction overnight with only a fractional drop in enantioselectivity (entry 4). For practical reasons, this reaction was run with a tenfold dilution in catalyst concentration to 1.9 mM.





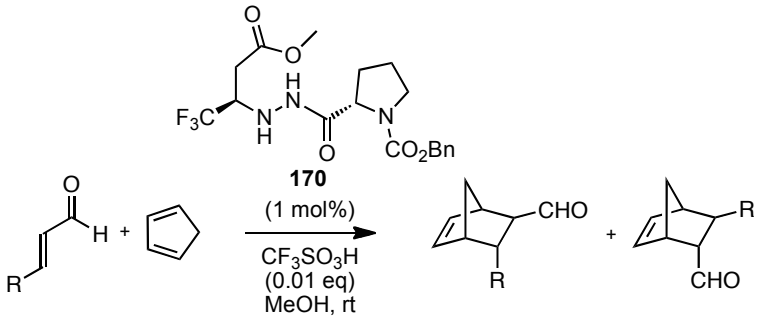
(5*R*)-163 **84** **170**

Entry	Catalyst	Time (h)	Yield (%)	*exo:endo*	*exo* % ee	*endo* % ee
1	**(5*R*)-163**	4	84	35:65	65	73
2	**84**	24	82 (conv.)	50:50	-	-
3	**170**	4	81	37:63	62	81
4[a]	**170**	18	71	35:65	60	79

Table 5.5: Variation of catalysts
a) 1mol% catalyst loading (1 mol% triflic acid)

Such a low catalyst loading, while more common in transition metal-based systems, is unusual in organocatalysis, particularly within the sphere of iminium ion catalysis.[44] For this reason, we next set out to ascertain whether the high activity of acyclic catalyst **170** would be maintained with different aldehydes. The results with a small range of different aldehydes are outlined in Table 5.6, with the *endo* enantioselectivity for each substrate when catalyst **(5*R*)-163** was employed included for comparison (see Table 5.4). The diastereoselectivity ratios for all substrates were found to be approximately identical to those observed with **(5*R*)-163** as catalyst. A small increase in enantioselectivity was observed in most cases, particularly so in the case of 4-methoxycinnamaldehyde where the *endo* ee increased from 77 % to 86 %, the highest observed in this series (entry 3). The exceptions were 4- and 2-nitrocinnamaldehyde which

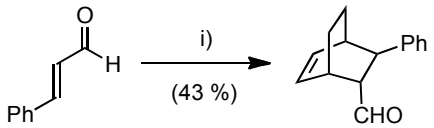
showed essentially no change in enantioselectivity when **170** was used as catalyst compared to **(5*R*)-163** (entries 3 and 4).[107] With aliphatic aldehydes, catalyst **(5*R*)-163** had generally given lower enantioselectivities than with aromatic substrates. While still modest, catalyst **170** showed an improved *endo* ee with aliphatic aldehyde (*E*)-2-hexen-1-al of 54 %, compared to only 46 % with **(5*R*)-163** (entry 6).



Entry	R	Yield (%)	*exo:endo*	*exo* % ee	*endo* % ee	*endo* % ee (cat (5*R*)-163)
1	Ph	71	35:65	60	79	73
2	1-Nap	83	21:79	62	81	73
3[a]	4-OMe-C_6H_4	86	36:64	71	86	77
4[b]	4-NO_2-C_6H_4	91	36:64	62	75	77
5[b]	2-NO_2-C_6H_4	74	15:85	67	83	84
6	Pr	90	31:69	38	54	46
7	CO_2Et	65	44:56	5	13	10

Table 5.6: Diels-Alder reaction catalysed by **170**
a) Reactions at 5 ºC; b) 5 mol% catalyst loading

The reaction of cinnamaldehyde and cyclohexadiene was also re-tested with 10 mol% catalyst **170** and it was found that ***endo*-(2*R*)-118** was again the major product (*exo*:*endo* 6:94) and was isolated in an improved 43 % yield after just 3 days with an identical enantioselectivity to that of **(5*R*)-163** (Scheme 5.7).



37 ***endo*-(2*R*)-118** (85 % ee)

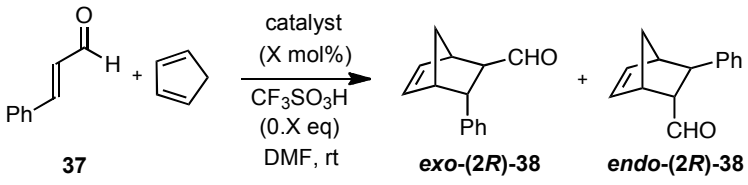
Scheme 5.7: *Reagents and conditions*: i) 10 mol% **170**, 10 mol% triflic acid, cyclohexadiene, methanol, rt, 3 days.

5.3 Investigations into active catalyst species

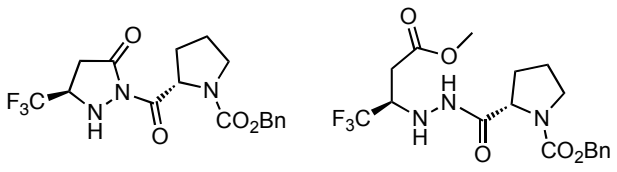
It was now clear that catalyst **170** was a highly active and enantioselective iminium ion catalyst, with diastereo- and enantioselectivities very similar to those found when catalyst **(5*R*)-163** was used. This raised the issue of whether **170** represented the single active catalytic component even when catalyst **(5*R*)-163** was employed or whether the observed turnover was as a result of a combination of both catalysts acting simultaneously. Unfortunately, time constraints have

meant that a full exploration of the relative rates of the two catalysts has not been possible. Preliminary investigations to establish a general trend have been undertaken and are outlined in the following section.

Establishing the reaction rate of catalyst **(5*R*)-163** is challenging due to its rapid conversion to catalyst **170** under the established reaction conditions. It was hoped to partially overcome this issue by changing to a non-nucleophilic solvent, thereby eliminating the possibility of nucleophilic attack on the pyrazolidinone ring. DMF was selected as an alternative solvent due to its similar dielectric constant (38 compared to 33 for methanol)[108] and the results with both catalysts in DMF are outlined in Table 5.7. While both catalysts showed reduced reactivity compared to their respective reactions in methanol, catalysis by 10 mol% **(5*R*)-163** was particularly sluggish, with only a 25 % yield of *exo* and *endo* products after 48 h (entry 1). In addition, the enantioselectivities were significantly lower than in methanol at 21 % and 38 % for *exo* and *endo*, respectively. By comparison, 1 mol% of catalyst **170** gave a superior yield of products after 24 h (40 %) while maintaining good enantioselectivity (entry 2). These results indicate **(5*R*)-163** was in and of itself not an effective catalyst.



37 ***exo*-(2*R*)-38** ***endo*-(2*R*)-38**

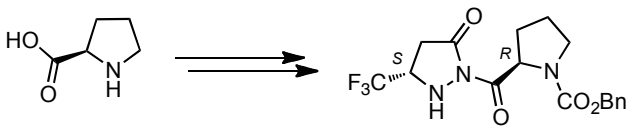


(5*R*)-163 **170**

Entry	Catalyst	Rxn. Time (h)	Loading (mol%)	Yield (%)	*exo:endo*	*exo* % ee	*endo* % ee
1	**(5*R*)-163**	48	10	25	45:55	21	38
2	**170**	24	1	40	41:59	57	69

Table 5.7: Diels-Alder reactions catalysed by **(5*R*)-163** and **170**

In an effort to quantify the relative rates of reaction of ring-closed catalyst **(5*R*)-163** and ring-opened catalyst **170** in methanol itself, the use of competition experiments was investigated. For this purpose, the enantiomer of catalyst **(5*R*)-163** was synthesised, using the established synthetic route, from D-proline (Figure 5.9).



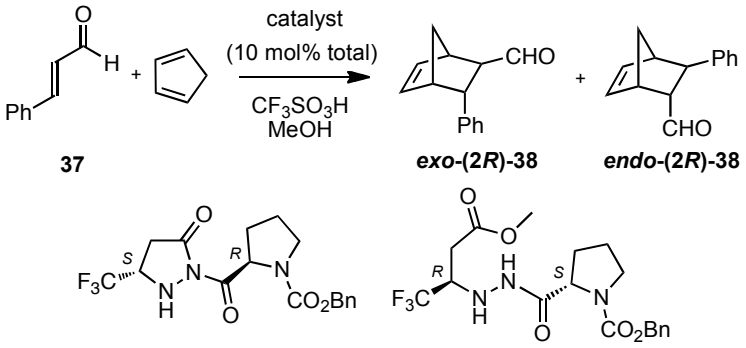
14*
D-proline

(5*S*)-163*

Figure 5.9: Conversion of D-proline **14*** to **(5*S*)-163***

It was confirmed that **(5*S*)-163*** gave the opposite absolute configuration in Diels-Alder adducts ***exo-*** and ***endo*-38** ((2*S*) as opposed to (2*R*)) by performing a reaction at 10 mol% catalyst loading (Table 5.8, entry 1). With this in mind, a series of experiments in which varying mixtures of **(5*S*)-163*** and **170** (always amounting to 10 mol% in total) were used to catalyse the reaction of (*E*)-cinnamaldehyde **37** and cyclopentadiene and the results are outlined in Table 5.7. With each catalyst favouring the opposite enantiomer of the products, the ee of the products served as a partial measure of the relative reaction rates of the two species. This was complicated somewhat by the knowledge that **(5*S*)-163*** was inevitably undergoing ring-opening during the experiments, leading to the formation of the enantiomeric catalyst of **170**. Nonetheless, the experiments were deemed valuable as a qualitative measure of reactivity (the results with acyclic hydrazide **170** are included for reference, see entry 2).

When a 1:1 mixture of **(5*S*)-163*** and **170** was used, the observed ee of the *endo* diastereoisomer was 68 % in favour of the (2*R*)-enantiomer (entry 3). This was consistent with that catalyst **170**, which favours the (2*R*)-enantiomer, displaying a higher rate of catalytic turnover than **(5*S*)-163***. It should be noted that the ee had decreased by 13 % in comparison to the use of **170** only (see entry 2), indicating some contribution from **(5*S*)-163*** to catalysis. This is more obvious when a 9:1 mixture of **(5*S*)-163*** and **170** was employed (entry 4). The ee reduced substantially to 50 %, though the (2*R*)-enantiomer was still favoured indicating the dominance of **170** as a catalyst, even at 9 times lower concentration than its ring-closed counterpart. These results would imply that catalyst **170** is sufficiently reactive to be the major source of catalytic turnover even at low concentrations. Nonetheless, there is likely also a contribution from **(5*R*)-163** itself.



Entry	(5*S*)-163*:170 (mol%)	Yield (%)	*exo:endo*	*endo* % ee[a]
1	10:0	96	36:64	–68
2	0:10	81	37:63	81
3	5:5	93	38:62	68
4	9:1	95	37:63	50
5	9.5:0.5	92	36:64	27

Table 5.8: Competition experiments between **(5*S*)-163*** and **170**
a) negative ee refers to (2*S*) enantiomer

In order to better understand the difference in turnover rates between catalysts **(5*R*)-163** and **170**, monitoring experiments were run in deuterated methanol and followed by ^{1}H NMR spectroscopy. In both cases, 1-methylnaphthalene was used as a reaction standard and this allowed straightforward calculation of reaction concentration. In order to achieve reactions with rates convenient to ^{1}H NMR spectroscopic monitoring, the reaction with catalyst **(5*R*)-163** was run at 4 mol% catalyst loading (76 mM) and reaction with **170** at 2 mol% loading (38 mM). A typical ^{1}H NMR spectra from the experiment is shown in Figure 5.10.

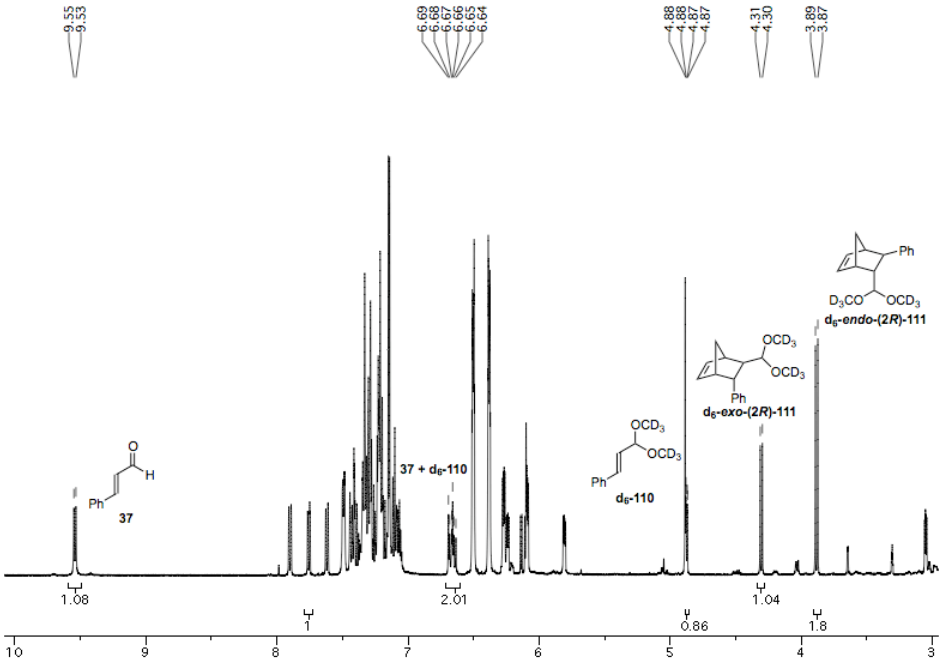


Figure 5.10: Typical ^{19}F NMR spectra from Diels-Alder reaction catalysed by **170**

The concentrations of (*E*)-cinnamaldehyde **37** and di-CD_3 acetals **110**, ***exo*-(2*R*)-** and ***endo*-(2*R*)-111** were monitored over the course of 4.5 h (Figure 5.11). It was found that (*E*)-cinnamaldehyde and the corresponding acetal **d_6-110** were present in both reaction mixtures at all times, in an approximately constant ratio of 1.1:1 aldehyde:acetal. By contrast, only the di-CD_3 acetals ***exo*-(2*R*)-** and ***endo*-(2*R*)-174** were observed and never the parent aldehydes.[106]

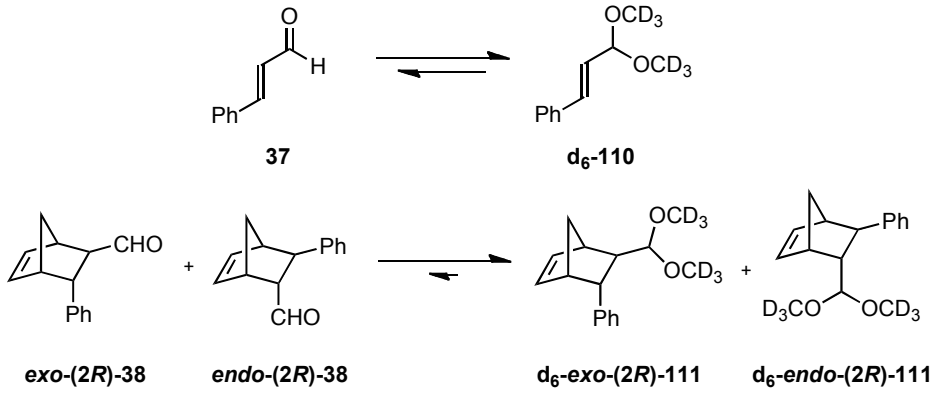


Figure 5.11: Equilibria of di-CD_3 acetals to aldehyde in CD_3OD

Of most relevance to this discussion is the combined rate of formation of di-CD_3 acetal products ***exo*-(2*R*)-** and ***endo*-(2*R*)-174** and this is represented graphically in Figure 5.12. The rate of formation with catalyst **170** is appreciably faster than with **(5*R*)-163**- after 256 min (4.27 h), reaction with 4 mol% **(5*R*)-163** reached 76 % conversion (relative to the internal standard) whereas catalysis with 2 mol% **170** gave 75 % conversion in just 98 min (1.63 h).

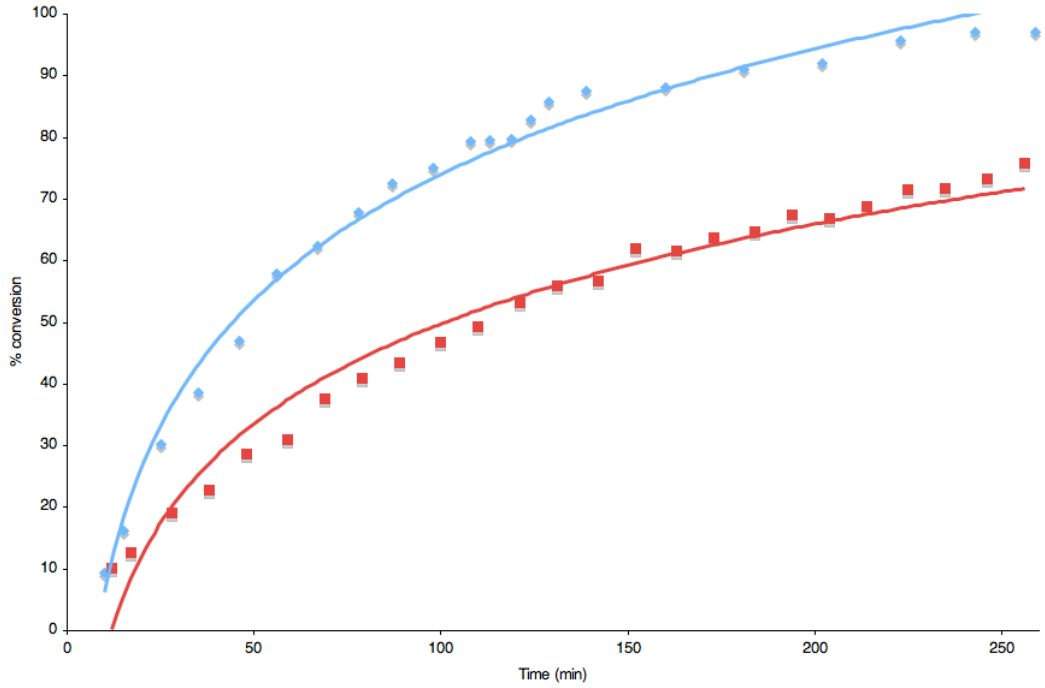


Figure 5.12: Graph of % conversion (against standard) vs. time (min) for Diels-Alder reactions catalysed by **(5*R*)-163** (red) and **170** (blue)

It is clear from this and the other experiments undertaken to date that ring-opened catalyst **170** represents a highly reactive catalyst and is significantly more reactive than ring-closed catalyst **(5*R*)-163**. Catalyst **170** also retains high reactivity at low catalyst loadings and, crucially, low catalyst concentration. However, full characterisation of the contribution of the two species to catalysis under standard reaction conditions remains challenging for a number of reasons. These include:

- The large variation in the concentrations of **(5*R*)-163** and **170** over the timecourse of the reaction.
- The potential for different rates of iminium formation and subsequent cycloaddition with each catalyst.

Despite these obstacles, studies thus far have strongly indicated that **170** makes the dominant contribution to catalysis, even when present at low concentrations relative to **(5*R*)-163**.

5.4 Summary

Asymmetric reaction with catalyst **(5*R*)-163** was optimised and the catalyst was subsequently screened against a range of α,β-unsaturated aldehydes. Good ee's were obtained for a variety of aromatic aldehydes but aliphatic aldehydes were less selective. **(5*R*)-163** was also found to catalyse the reaction of (*E*)-cinnamaldehyde and cyclohexadiene with low turnover but good enantioselectivity. The (2*R*)-enantiomer was preferred for all *exo* and *endo* adducts and this led us to investigate the geometry of the key iminium ion intermediate. Racemic catalyst **114** was used as a model system and an iminium ion **169** was isolated from reaction in methanol. **169** was found to have (*Z*)-geometry in the key N=C bond, consistent with the observed product stereochemistry, but also to have undergone ring-opening due to acid catalysed methanolysis of the pyrazolidinone ring. Chiral catalyst **(5*R*)-163** was found to undergo a similar methanolysis under the reaction conditions at a rate comparable to the rate of product formation. One of the methanolysis products, chiral acyclic hydrazide **170**, was readily isolated and found to be a highly active catalyst, effective at catalyst loadings as low as 1 mol%. Competition experiments and ^{1}H NMR spectroscopy monitoring experiments indicated that **170** likely represents the key active catalytic species in reactions employing **(5*R*)-163**.

5.5 Future work

Future efforts in this area would look to elucidate the mechanism of action of ring-opened catalyst **170**. Key to this would be isolation of iminium ion **173**, derived from **170**, and

information gathered from such a structure would be invaluable in understanding how the acyclic structure still successfully imparts good levels of diastereo- and enantioselectivity (Figure 5.13a)). The implications of the isolation of **170** on the catalytic mechanism of the other diastereoisomeric series have also not yet been investigated. That a similar ring-opening process has taken place with related compounds tested seems likely but has not been unambiguously established (Figure 5.13b)). Isolation and testing of the respective hydrazides, such as **174** derived from methylmandelic acid **(5*S*)-134**, may furnish new catalysts with high levels of reactivity/stereoselectivity.

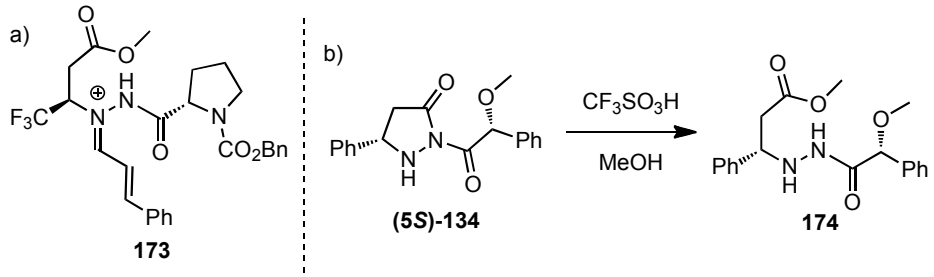


Figure 5.13: a) Iminium ion derived from hydrazide **173**; b) Methanolysis of **(5*S*)-134** to **174**

With the optimal catalyst established, it could then be applied to other iminium ion processes, such as Friedel-Crafts alkylation (Figure 5.13).

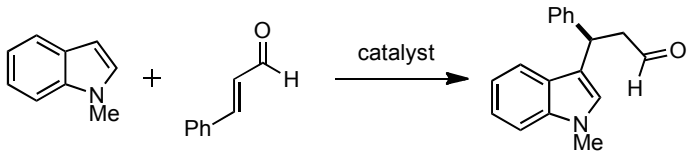


Figure 5.14: Iminium ion catalysed Friedel-Crafts alkylation

Chapter 6: The Steglich rearrangement of pyrazolin-3-ones

The suitability of pyrazolin-3-ones as substrates in an organocatalysed *O*- to *C*- carboxyl transfer process was explored. A model pyrazolinone substrate with *N*(2)-phenyl and *C*(5)-methyl substitution underwent rearrangement to a mixture of starting material *C*(4)-carboxylate, *N*(1)-carboxylate and parent pyrazolinone when treated with a series of Lewis base catalysts. Of these catalysts, DMAP, isothiourea DHPB and a triazolium N-heterocyclic carbene (NHC) were tested with a series of phenyl and/or methyl substituted pyrazolinones and the subsequent product distributions analysed. While the NHC catalyst generally gave *C*-carboxylation, DMAP and DHPB favour *N*-carboxylation, particularly at short (1 h) reaction times. The *N*-carboxylates arising from three of these pyrazolinones were isolated and re-exposed to catalyst in order to begin to rationalise the observed product distributions. These results were then applied to the development of an asymmetric protocol using chiral NHCs as catalysts and preliminary results are presented.

6.1 Introduction

The *O*- to *C*- carboxyl group transfer of oxazolyl carbonates to the corresponding α- or γ-carboxyazlactone, catalysed by either DMAP or PPY, was first described by Steglich and Höfle in 1970 (Figure 6.1).[109] The α-carboxyazlactone product was found to be generally favoured unless R^2 was a strongly electron-withdrawing substituent (e.g. R^2 = CF_3 or 4-$O_2NC_6H_4$) or the α-position was highly sterically encumbered (e.g. R^1 = *t*-Bu).

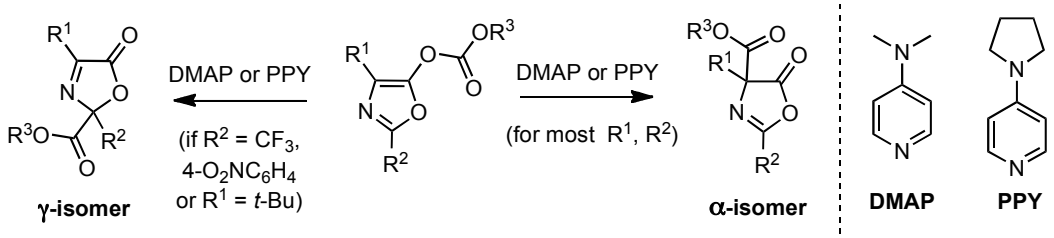


Figure 6.1: Steglich rearrangement of 5-oxazolyl carbonates

A basic catalytic cycle for this reaction is outlined in Figure 6.2. Attack on carbonate **A** by the catalyst (DMAP or PPY) generates a tetrahedral intermediate **B** which, on breakdown, gives the key ion pair of dienolate **C** and carboxylated catalyst **D**. Recombination of this ion-pair can occur at either the α- or γ-positions to generate the α- or γ-carboxyazlactone products, respectively.

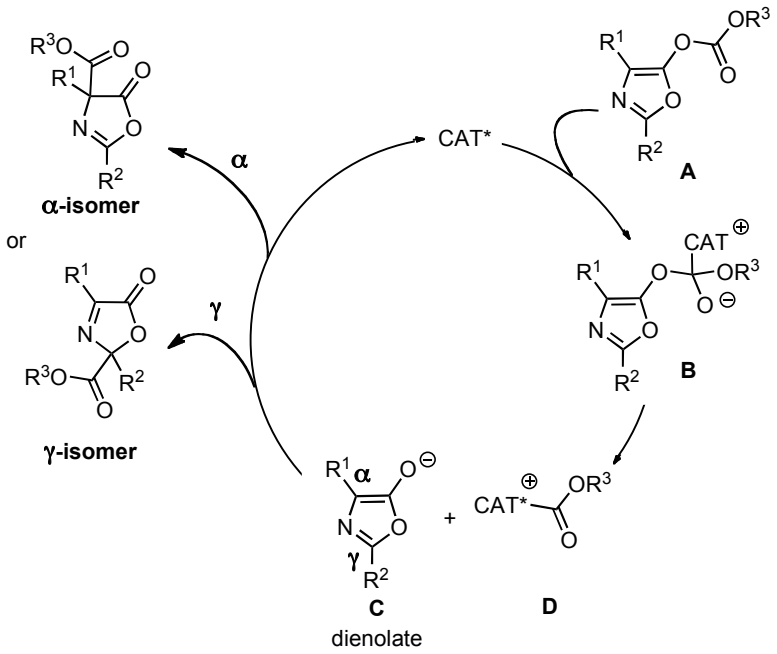


Figure 6.2: Catalytic cycle of Steglich rearrangement of 5-oxazolyl carbonates

More recent investigations into the Steglich rearrangement have focused on an enantioselective variant of this reaction.[110] The groups of Fu,[111] Vedejs[112] and Richards[113] have shown that the chiral DMAP or PPY derivatives, shown in Figure 6.3, induce high enantioselectivity in the rearrangement. Examples of other enantioselective catalyst classes include phosphines by Vedejs,[112] ammonium betaines by Ooi[114] and bicyclic imidazoles developed by Zhang.[115] The Smith group have investigated N-heterocyclic carbenes[116] and isothioureas as both racemic and chiral catalysts.[117] Selected results employing both these series of catalysts are outlined in the following section.

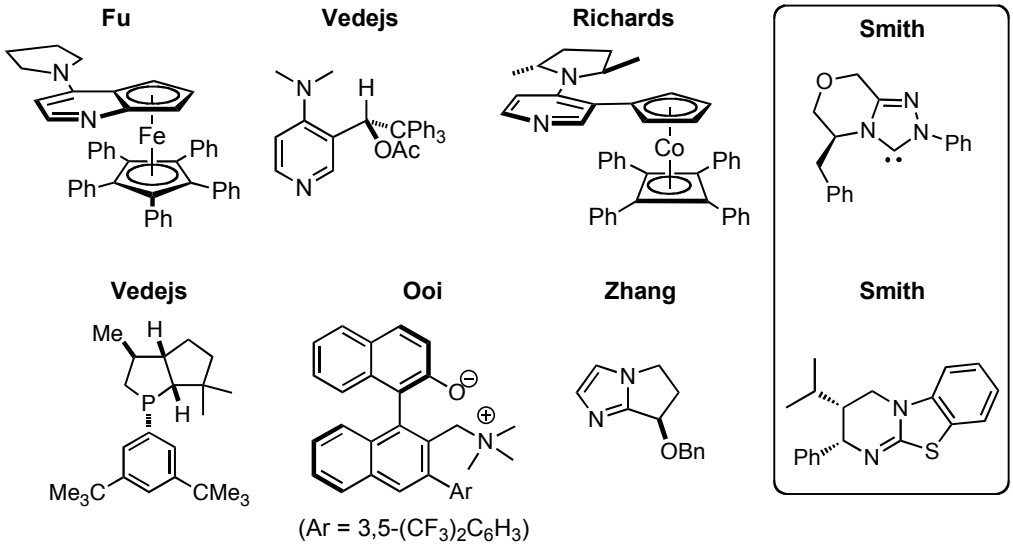
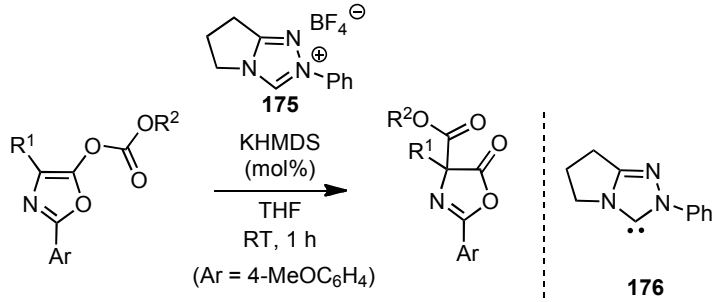


Figure 6.3: Selected catalysts of the asymmetric Steglich rearrangement

6.1.1 N-heterocyclic carbenes as catalysts

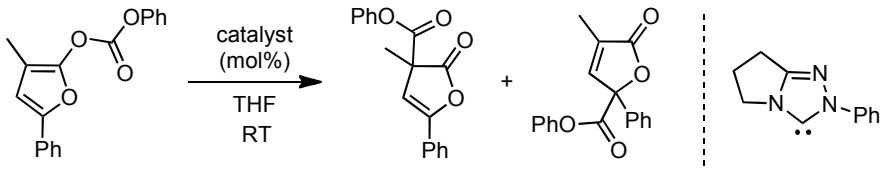
The catalytically efficient racemic carboxyl transfer of 5-oxazolyl carbonates can be achieved using NHC-mediated catalysis.[118,119] For example, NHC **176**, generated *in situ* from triazolium salt **175** and KHMDS as base promotes the *O*- to α-*C*-carboxyl transfer (no γ-isomer observed in this case) with a range of substrates at low catalyst loading (0.9 mol%, Table 6.1). A slight excess of triazolium salt was used relative to the KHMDS in order to ensure no free base was present. A range of substitution patterns were readily tolerated, in particular, α-branching at C(4) is well tolerated in contrast to the majority of catalysts in Figure 6.3, which are unable to rearrange such substrates (entry 4). Crossover experiments were used to prove that the C-C bond forming event was irreversible.[116,120]



Entry	R^1	R^2	Loading (mol%)	[Catalyst] (mM)	Yield (%)
1	Me	Ph	0.9	4	82
2	Bn	Ph	0.9	4	80
3	Bn	Me	0.9	4	82
4[a]	*t*-Bu	Ph	4	5	73

Table 6.1: Rearrangement of oxazolyl carbonates by NHC **176**
a) Reaction time 2 h

Since the initial reports on oxazolyl carbonates, work within the Smith group has employed alternate heterocyclic substrates such as benzofuranyl and indolyl carbonates using NHC-mediated catalysis.[121,122] For the *O*- to *C*- carboxyl transfer of furanyl carbonates, both DMAP and NHC **176** were shown to be effective catalysts but gave differing mixtures of α- and γ- products (Table 6.2).[123] DMAP modestly favoured the α-isomer **178** (entry 1) whilst NHC **176** favoured the γ-isomer **179** with high regiocontrol (entry 2). Upon lowering the loading and concentration of NHC, almost complete γ-selectivity was observed (entry 3).



Entry	Catalyst	Loading (mol%)	[Catalyst] (mM)	Ratio (α:γ)
1	DMAP	10	34	60:40
2[a]	**176**	10	34	16:84
3[a]	**176**	0.9	3.4	<2:>98

Table 6.2: Treatment of furanyl carbonate **177** with DMAP and **176** at different concentrations
a) Catalyst generated *in situ* from triazolium salt **175** and KHMDS

Furthermore, independent treatment of the individual regioisomers with NHC **176** at 31 mM gave rise in each case to an essentially identical 15:85 α:γ mixture of the two regioisomers (Figure 6.4). This implies that *C*-carboxylation under NHC catalysis in this system is reversible, in contrast to that observed with oxazolyl carbonates, with the γ-product favoured at equilibrium.

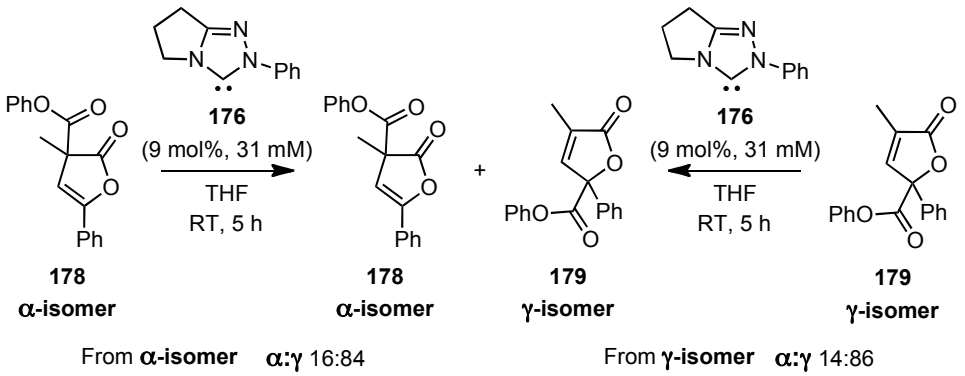


Figure 6.4: Re-treatment of α-isomer **178** and γ-isomer **179** with NHC **176**

Recently, an enantioselective variant of the *O*- to *C*- carboxyl transfer of oxazolyl carbonates has been investigated.[116] A structurally diverse selection of chiral azolium catalysts were tested with representative examples given in Figure 6.5. Triazolium derived catalysts, such as **184**-**186**, gave high conversion to exclusively *C*-carboxylated product **181** and generally higher enantioselectivities (though poor) than imidazolium and imidazolinium-derived catalysts (e.g. **187**). Imidazolinium catalysts, such as **187**, produced a mixture of *C*-carboxylated product **181**, parent azlactone **182** and diphenyl carbonate **183** in catalysis.

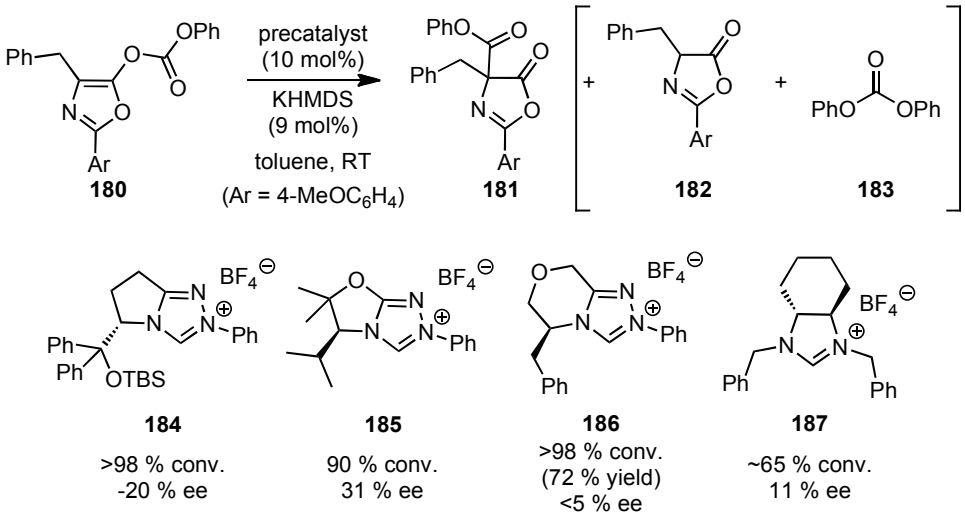


Figure 6.5: Rearrangement of oxazolyl carbonates by chiral NHCs

A complete and unambiguous hypothesis by which azlactone **182** and diphenyl carbonate **183** are produced under NHC catalysis has not yet been developed. However it can be assumed that *in situ* formation of phenoxide must be occurring to produce diphenyl carbonate **183**.[124] It has been postulated that phenoxide could be generated from collapse of **188** and **189**, which represent tetrahedral intermediates within the proposed catalytic cycle (Figure 6.6a)). Partial evidence for the role of phenoxide came from treatment of oxazolyl carbonate **181** with potassium phenoxide and 18-crown-6 which generated a mixture of pyrazolinone **182** and diphenyl carbonate **183** (Figure 6.6b)).

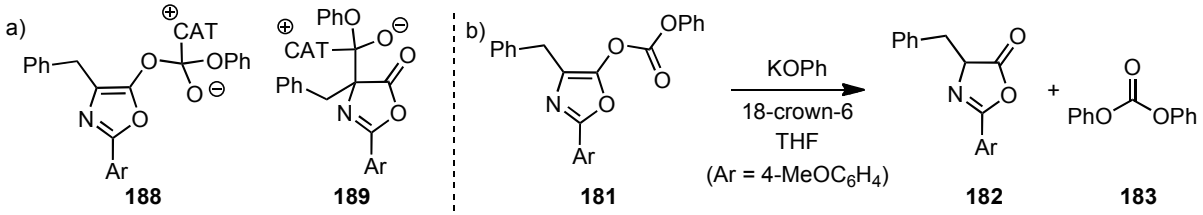


Figure 6.6: a) Tetrahedral intermediates that could act as sources of phenoxide; b) Reaction of **181** with potassium phenoxide

6.1.2 Isothioureas as catalysts

While investigating alternative bases for carbene generation in the above reactions, it was found that amidine bases could themselves act as catalysts of the Steglich rearrangement of oxazolyl carbonates (Figure 6.7).[124] While 6:7 ring-fused DBU gave modest conversion to parent pyrazolinone and diphenyl carbonate only, changing to 6:5 ring-fused DBN resulted in a significant change in product distribution with α-*C*-carboxylate product **181** now favoured (**181**:**182** 90:10). These initial findings prompted investigations into related catalytic architectures leading to the identification of cyclic isothiourea DHPB as an efficient achiral

catalyst for the rearrangement of oxazolyl and furanyl carbonates.[124,125] For example, the rearrangement of carbonate **181** can be realised in excellent yield with just 2 mol% catalyst loading. Chiral analogues of DHPB, such as **190** and **191**, were then found to be highly enantioselective catalysts of the Steglich rearrangement.[117] For example, the same rearrangement with catalyst **191** can be realised at –60 ºC in 93 % yield and 96 % ee.

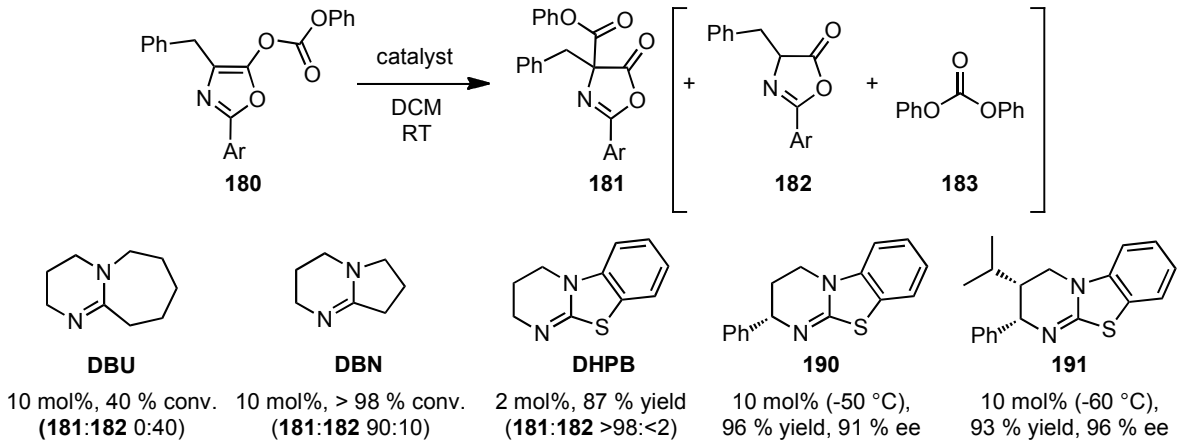


Figure 6.7: Rearrangement of substrate **181** by amidines and isothioureas (Ar = 4-$MeOC_6H_4$).

Mechanistic studies, including isolation of a carboxylated isothiouronium intermediate **192** and reaction monitoring, were employed to confirm the reversibility of *O*-carboxylation and the irreversibility of the key *C*-carboxylation step (Figure 6.8a)).[126] DFT calculations at the B3LYP/6-31G(d,p) theory level were performed on the reaction transition state to rationalise the observed high enantioselectivities (Figure 6.8b)).[117] In this rationale, the phenyl stereodirecting group is forced into a pseudoaxial position by the *N*-carboxyl group which is assumed to lie co-planar with the rest of the heterocycle. Facial selectivity on the dienolate is then controlled by a combination of steric factors and charge matching.

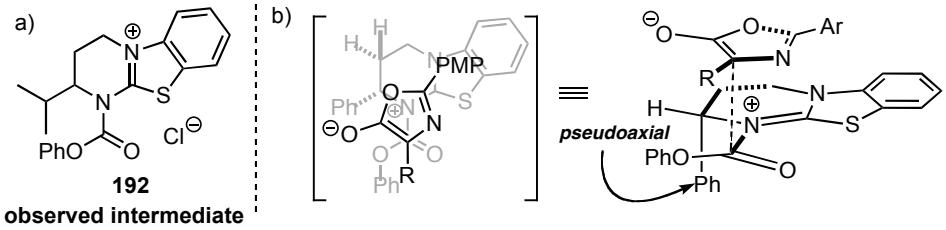


Figure 6.8: a) carboxylated isothiouronium intermediate **192**; b) Model of calculated reaction transition state for reaction with catalyst **190**

6.1.3 Pyrazolyl carbonates as substrates

Given our interest in the pyrazolidinone architecture, we wished to extend this methodology to the *O*- to *C*- carboxyl transfer of related pyrazolyl carbonates (Figure 6.9). To our knowledge, substrates of this type have never been tested as substrates in Steglich-type rearrangements.

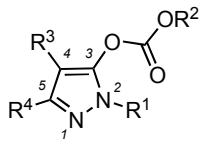
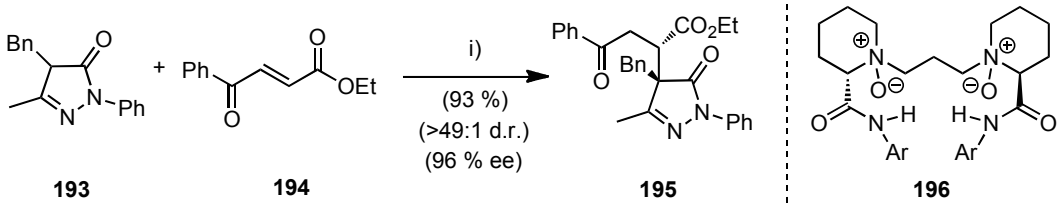


Figure 6.9: Generic structure of a pyrazolyl carbonate

A recent report by Feng *et al.* showed that pyrazolinones could be used as carbon-centered nucleophiles in an yttrium-catalysed Michael addition to δ-ketoesters (Scheme 6.1).[127,128] The reaction successfully forms two new stereocentres, with excellent stereocontrol, in the presence of chiral ligand **196**. Interestingly, it was observed that changing the metal from yttrium to scandium led to a reversal in the absolute configuration of the products.



Scheme 6.1: *Reagents and conditions*: i) 5 mol% $Y(OTf)_3$, 5.5 mol% **196**, DCM, 0 ºC, 48 h.
(Ar = 2,4,6-trimethylphenyl)

Although our potential catalytic system would be quite different, we were encouraged by the readiness of pyrazolinones to operate as carbon-centred nucleophiles (Figure 6.10). Our strategy would employ a similar mechanism to that observed with oxazolyl carbonates (see Figure 6.2) with dienolate **C** and carboxylate **D** generated *in situ* from pyrazolyl carbonate **A**. Recombination could then occur either α- or γ- to the carbonyl to give *C*-carboxylate **E** or *N*-carboxylate **F**, respectively. If conditions could be found to control the regioselectivity of the process to favour α-enolate reactivity, this would then allow rapid access to highly functionalised pyrazolinones containing a quaternary stereocentre, which would be of significant biological interest.[129]

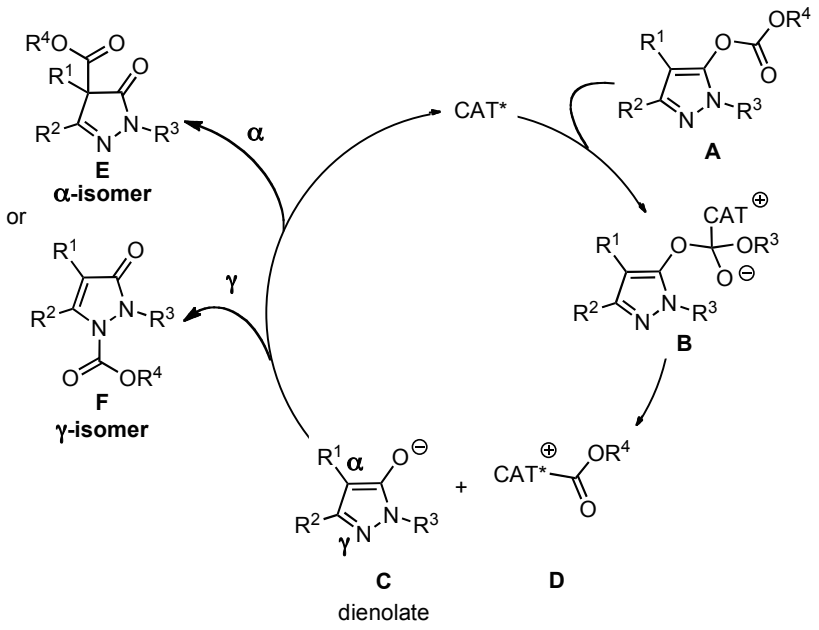


Figure 6.10: Proposed catalytic cycle for the Steglich-type rearrangement of pyrazolyl carbonates

6.2 Proof of concept

Initial investigations focused on establishing whether pyrazolyl carbonates were suitable substrates for Steglich-type rearrangement reactions. Parent pyrazolinone **198** was readily prepared from the commercially available ketoester **197** and phenylhydrazine (Scheme 6.2). Compounds such as **198** have three possible tautomeric forms: **198** (CH), **198′** (NH) and **198″** (OH) and the ratio of these forms can vary with temperature, solvent etc. (Figure 6.11).[130,131] In the case of pyrazolinone **198**, a 5:1 mixture of tautomers **198** and **198′** was observed on ^{1}H NMR spectroscopic analysis in $CDCl_3$.

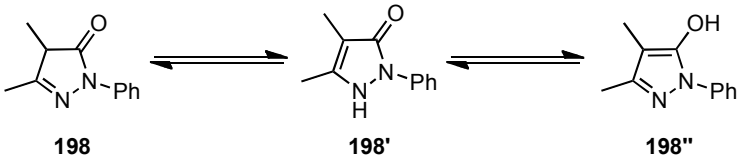
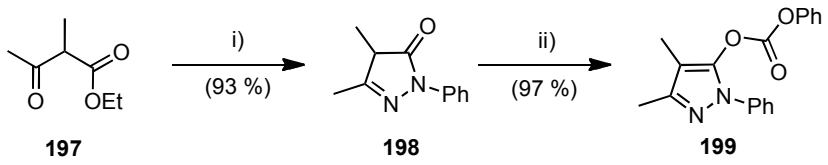


Figure 6.11: Potential tautomeric forms of pyrazolinone **198**

Fortunately, the presence of these isomeric forms in solution did not appear to hinder carbonate formation, with model substrate **199** obtained in 97 % yield after treatment of **198** with phenyl chloroformate. The site of carboxylation for this, and related compounds, was established by a combination of ^{1}H and ^{13}C NMR spectroscopy and is discussed in Section 6.2.1.



Scheme 6.2: *Reagents and conditions*: i) phenylhydrazine, ethanol, reflux; ii) triethylamine, phenyl chloroformate, THF, 0 °C to rt.

Pleasingly, treatment of carbonate **199** with DMAP resulted in significant levels of rearrangement after just 1 h, as judged by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Table 6.3, entry 1). The major product after this period was assigned as the *N*-carboxylate **201**, making up 65 % of the reaction mixture while the desired *C*-carboxylate **200** was formed in only trace quantities (5 %). In a repeat reaction, *N*-carboxylate **201** was isolated from an essentially identical mixture in 56 % yield and a crystal structure obtained to corroborate the assigned structure (Figure 6.12).

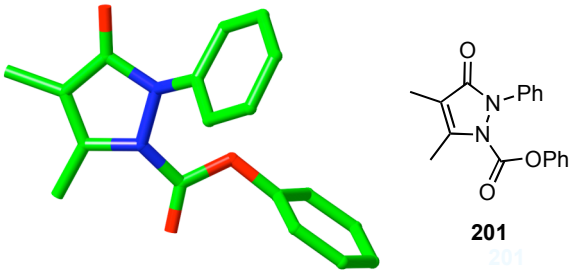
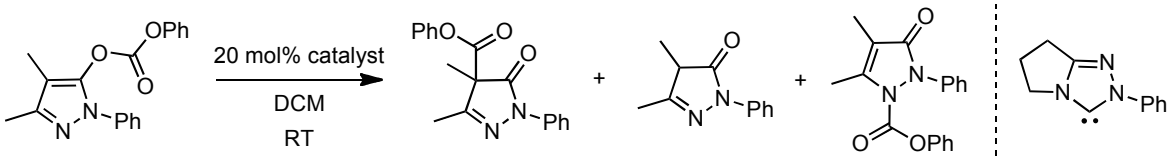


Figure 6.12: Molecular representation of the single crystal structure of **201**

Re-treatment of this reaction mixture with DMAP overnight, led to near completion (98 % conversion) and *C*-carboxylate **200** was now the major product (42 % isolated yield, entry 2). Similar product distributions were obtained after 1 h when PPY was used as the catalyst (entry 3). The results when DHPB were used follow a similar trend but it was noted that, at longer reaction times, the major component was the parent pyrazolinone **198** (entries 4 and 5).

In contrast, when the NHC **176** (generated from the appropriate triazolium salt and KHMDS) was used in THF, reaction was complete in just 1 h with *C*-carboxylate **200** as the major product, isolated in 65 % yield (entry 6). Levels of parent compound formation were low (17 %) and no *N*-carboxylate could be observed. In order to verify that this change in product distribution was due to the change in catalyst and not solvent, a reaction using DMAP as catalyst in THF was run (compare entries 2 and 7). It was found that levels of product **200** in THF were slightly lower (62 % in DCM against 45 % in THF) although this appeared to be a result of a lower reaction rate in THF (90 % conversion against 98 % in DCM).[132]

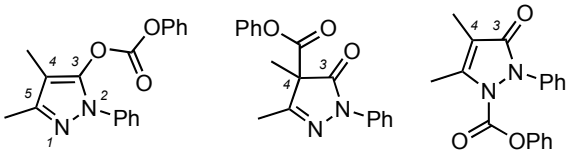


Entry	Catalyst	Time (h)	% Ratio				200 yield (%)
			199	200	198	201	
1	DMAP	1	27	5	3	65	
2	DMAP	o/n	2	62	25	11	42
3	PPY	1	8	4	8	80	
4	DHPB	1	34	6	2	58	
5	DHPB	o/n	6	13	64	17	
6[a,b]	**176**	1	0	83	17	0	65
7[a]	DMAP	o/n	10	45	15	30	

Table 6.3: Rearrangement of pyrazolyl carbonate **199**-ratio of products
a) Reaction solvent = THF
b) **176** derived from *in situ* deprotonation of triazolium salt **175** with KHMDS

6.2.1 Identification of site of carboxylation

The three isomeric products resulting from carboxylation of parent pyrazolinone **198** were unambiguously assigned by a combination of ^{1}H and ^{13}C NMR spectroscopy (Table 6.4). *C*-carboxylate **200** (entry 2) is readily identified by the upfield shift of the *C*(4)-methyl group protons, relative to both *O*- (entry 1) and *N*-carboxylates (entries 1 and 3, respectively). A similar upfield trend upon *C*-carboxylation is also evident for the chemical shift of the C(4) atom in ^{13}C NMR spectroscopy. The *O*- and *N*-carboxylates can then be distinguished by the ^{13}C chemical shift of C(3); *O*-carboxylate **199** has a C(3) chemical shift consistent with an enol ester (141.6 ppm), whereas *N*-carboxylate **201** has a shift consistent with a ketone (167.9 ppm). These trends were used to identify the site of carboxylation for all the subsequent pyrazolinone substrates discussed in the following section.



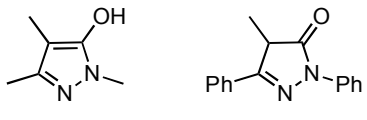
199 **200** **201**

Entry	Substrate	Chemical shift (ppm)		
		C(4)CH_3	*C*(3)	*C*(4)
1	**199**	2.00	141.6	104.3
2	**200**	1.73	170.4	61.6
3	**201**	1.93	167.9	111.0

Table 6.4: Selected ^{1}H and ^{13}C NMR chemical shifts for compounds **199**, **200** and **201**

6.3 Substrate optimisation

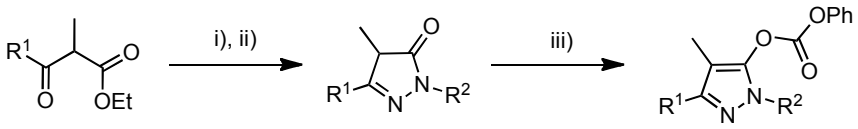
It had now been established that pyrazolyl carbonates could act as effective substrates in organocatalysed Steglich-type rearrangements. We next sought to investigate how other substituent patterns affected reactivity and regioselectivity. In particular, we focused on the substituents at C(5), adjacent to the reactive centre, and the substituent at N(1). To this end, three other pyrazolyl carbonates were prepared, using similar chemistry to that established for **199** (Scheme 6.3). Condensation of the appropriate hydrazine with an α-methyl β-ketoester in refluxing ethanol proceeded successfully in each case, although **205** required a second reflux in toluene to give good conversion and an isolated yield of 64 %.[133] As with *N*(2)-phenyl, *C*(5)-methyl compound **198**, each pyrazolinone gave a mixture of CH and NH tautomeric forms when analysed by ^{1}H NMR spectroscopy.[130,131] In contrast, upon IR spectroscopic analysis of the respective solids, di-phenyl substrate **205** was assigned as the CH form while di-methyl substrate **203** was identified as exclusively the OH tautomer **203″** (Figure 6.13).



203" **205**

Figure 6.13: Tautomers **203″** and **205″**

With the necessary precursors in hand, straightforward carbonate formation gave the desired products **206**–**208**. The structure of carbonate **207** was confirmed by crystal structure analysis (Figure 6.14).

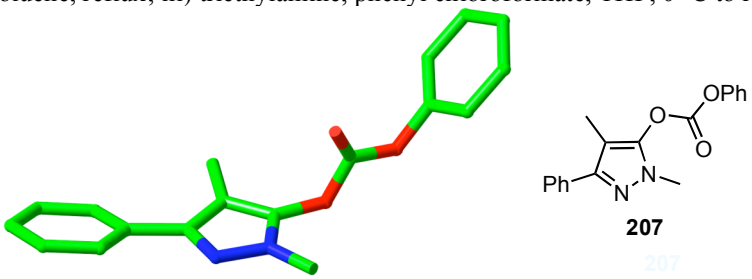


197, R^1 = Me
202, R^1 = Ph

203, R^1 = Me, R^2 = Me (85 %)
204, R^1 = Ph, R^2 = Me (64 %)
205, R^1 = Ph, R^2 = Ph (81 %)

206, R^1 = Me, R^2 = Me (59 %)
207, R^1 = Ph, R^2 = Me (90 %)
208, R^1 = Ph, R^2 = Ph (89 %)

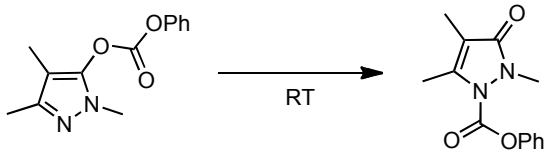
Scheme 6.3: *Reagents and conditions*: i) phenylhydrazine or methylhydrazine, ethanol, reflux; ii) (for **205** only) toluene, reflux; iii) triethylamine, phenyl chloroformate, THF, 0 ºC to rt.



207

Figure 6.14: Molecular representation of the single crystal structure of **207**

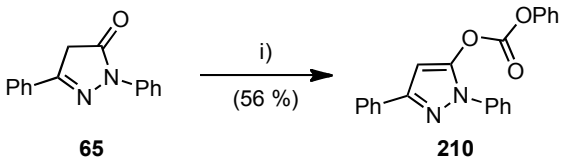
Interestingly, it was found that dimethyl substrate **206** underwent slow (> 24 h) rearrangement to *N*-carboxylate **209** upon standing at room temperature (Figure 6.15). This necessitated storage of the substrate at low temperature (5 ºC), which arrested the process. In addition, it was found that the parent pyrazolinone **203** was removed from the reaction mixture during acidic work-up. Hence, for di-methyl substrate **206** an alternative work-up was used in which the reaction mixture was concentrated *in vacuo* and then analysed directly by ^{1}H NMR spectroscopy.



206 **209**

Figure 6.15: Spontaneous rearrangement of **206** to **209** at room temperature

Also investigated briefly was the influence of the substituent at the reactive centre (the C(4)-position). For related oxazolyl carbonates the formation of a quaternary stereocentre at carbon is not just desirable but essential for successful Steglich rearrangement and we were interested if this was also the case in this series.[118] *C*(4)-Unsubstituted pyrazolinone **65** was already available as it had been synthesised previously within the group (see Section 2.1) and was converted to its pyrazolyl carbonate **210** in 56 % yield (Scheme 6.4). The influence of the methyl group at C(4) could then be inferred by comparison with the results of *C*(4)-methyl substrate **208**.



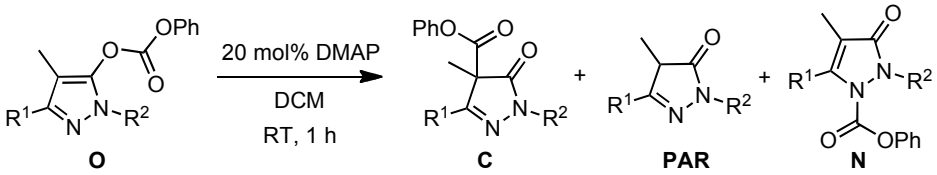
65 **210**

Scheme 6.4: *Reagents and conditions*: i) triethylamine, phenyl chloroformate, THF, 0 ºC to rt.

Each substrate was tested with DMAP, achiral isothiourea DHPB and the achiral NHC **176** and the results with each catalyst are outlined in the following section.

6.3.1 Testing of substrates

The results when each of the new substrates was treated with 20 mol% DMAP in DCM for 1 h are outlined in Table 6.5. Also included is the result under the same conditions for *N*(2)-phenyl, *C*(5)-methyl test substrate **199** (entry 1). Reactivity appeared strongly influenced by C(5) substitution, with *C*(5)-methyl substrates (entries 1 and 2) showing much higher reactivity than *C*(5)-phenyl (entries 3 and 4). In all cases, conversion was mainly to the *N*-carboxylate.



O **C** **PAR** **N**

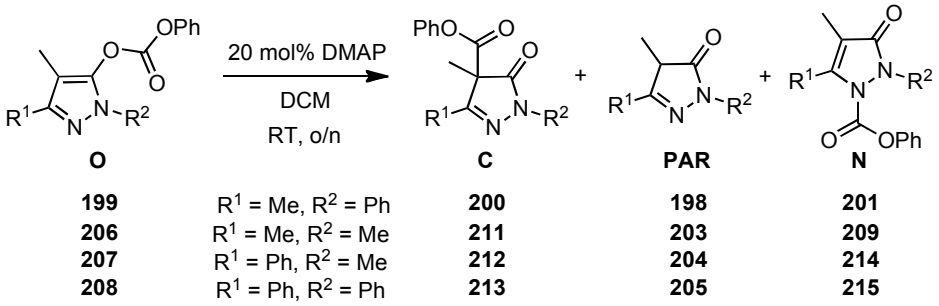
199	R^1 = Me, R^2 = Ph	**200**	**198**	**201**
206	R^1 = Me, R^2 = Me	**211**	**203**	**209**
207	R^1 = Ph, R^2 = Me	**212**	**204**	**214**
208	R^1 = Ph, R^2 = Ph	**213**	**205**	**215**

Entry	Substrate	R^1	R^2	% Ratio			
				O	**C**	**PAR**	**N**
1	**199**	Me	Ph	27	5	3	65
2	**206**	Me	Me	53	0	0	47
3	**207**	Ph	Me	83	0	2	15
4	**208**	Ph	Ph	79	5	4	12

Table 6.5: 1 h rearrangement of substrates with catalytic DMAP
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)

These reaction mixtures were then re-treated with DMAP overnight (apart from di-methyl substrate **206** where a separate overnight reaction was run) and the results are outlined in Table 6.6. Di-methyl carbonate **206** showed good conversion to almost exclusively the *N*-carboxylate (entry 2). *N*(2)-methyl, *C*(5)-phenyl carbonate **207** also favoured the *N*-carboxylate but with low 38 % conversion even with the extended reaction time (entry 3).

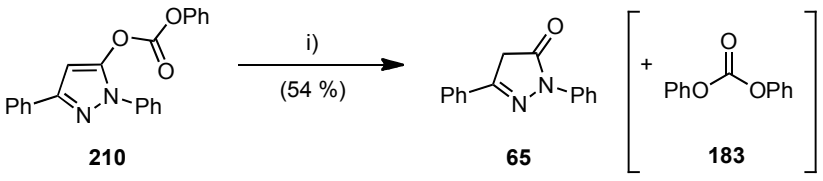
Better reactivity was observed with di-phenyl substrate **208** (78 % conversion), with the major component being rearrangement product, isolated in 24 % yield (entry 4).



Entry	Substrate	R^1	R^2	% Ratio				Yield (%)
				O	**C**	**PAR**	**N**	
1	**199**	Me	Ph	2	62	25	11	42 (**200**)
2	**206**	Me	Me	3	0	5	92	77 (**209**)
3	**207**	Ph	Me	62	2	6	31	14 (**214**)
4	**208**	Ph	Ph	22	42	32	4	24 (**213**)

Table 6.6: Overnight rearrangement of substrates with catalytic DMAP
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)

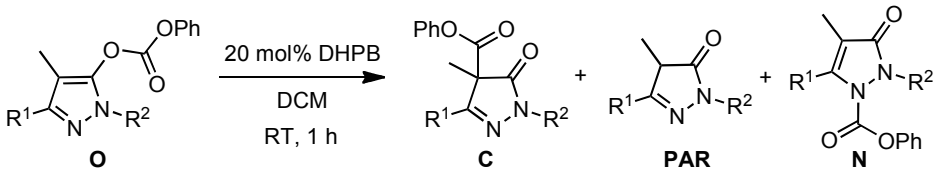
In contrast, treatment of C(4)-unsubstituted **210** with DMAP overnight gave full conversion to parent pyrazolinone **65**, as judged by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Scheme 6.5). **65** was isolated in 54 % yield along with diphenyl carbonate **183**. When a methyl group is present as in substrate **208**, the major component was *C*-carboxylated product **213** (see Table 6.6, entry 4). These results are consistent with the observation for oxazolyl carbonates that formation of a quaternary stereocentre at carbon is necessary for successful reaction with the absence of such a substituent leading only to return of the parent heterocycle.[118,119] However, the results did indicate that the first step of the catalytic cycle- the removal of the carbonate group by the nucleophilic catalyst- was proceeding with this substrate. DHPB was also tested as a catalyst under identical conditions and gave rise to a similar crude reaction mixture.



Scheme 6.5: *Reagents and conditions*: DMAP (20 mol%), DCM, rt.

The same substrates were next treated with 20 mol% DHPB in DCM and the results after 1 h are outlined in Table 6.7. The result for *N*(2)-phenyl, *C*(5)-methyl test substrate **199** is included

for reference (entry 1). Conversion levels were very similar to those obtained with DMAP (see Table 6.5) with the exception of di-methyl substrate **206** which showed almost complete conversion to the *N*-carboxylate (96 %, entry 2) compared to only 47 % with DMAP at the same timepoint.



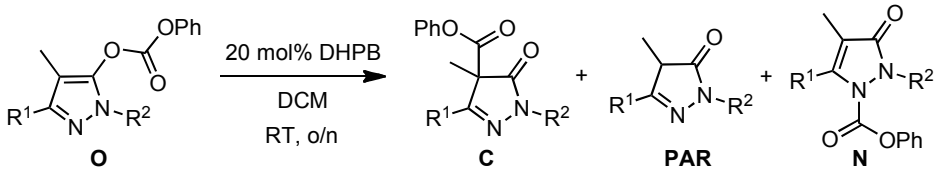
O **C** **PAR** **N**

199	R^1 = Me, R^2 = Ph	**200**	**198**	**201**
206	R^1 = Me, R^2 = Me	**211**	**203**	**209**
207	R^1 = Ph, R^2 = Me	**212**	**204**	**214**
208	R^1 = Ph, R^2 = Ph	**213**	**205**	**215**

Entry	Substrate	R^1	R^2	% Ratio			
				O	**C**	**PAR**	**N**
1	**199**	Me	Ph	34	6	2	58
2	**206**	Me	Me	3	0	1	96
3	**207**	Ph	Me	87	0	4	9
4	**208**	Ph	Ph	74	1	13	12

Table 6.7: 1 h rearrangement of substrates with catalytic DHPB
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)

In all but one case, carbonate cleavage to the parent pyrazolinone was the major outcome of treatment with DHPB overnight (Table 6.8). The *N*-carboxylate **209** remained the major product with di-methyl substrate **206** (61 %, entry 2) but this was a reduction on the quantity observed after 1 h, with a concomitant increase in the parent compound. These results imply that DHPB is generally less efficient than DMAP at re-delivering the carboxylate moiety to either carbon or nitrogen, though especially to carbon.

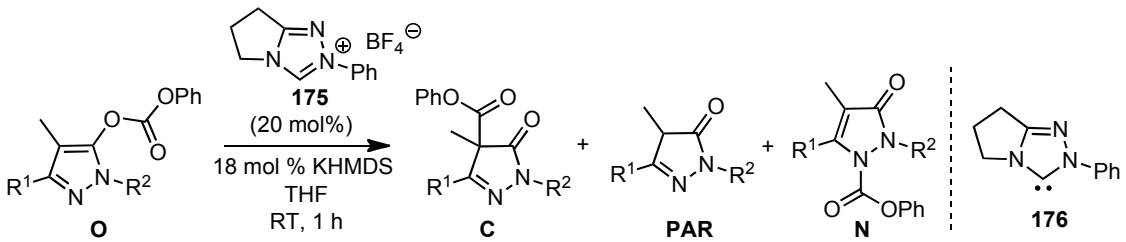


O		C	PAR	N
199	R^1 = Me, R^2 = Ph	**200**	**198**	**201**
206	R^1 = Me, R^2 = Me	**211**	**203**	**209**
207	R^1 = Ph, R^2 = Me	**212**	**204**	**214**
208	R^1 = Ph, R^2 = Ph	**213**	**205**	**215**

Entry	Substrate	R^1	R^2	% Ratio			
				O	**C**	**PAR**	**N**
1	**199**	Me	Ph	6	13	64	17
2	**206**	Me	Me	3	0	36	61
3	**207**	Ph	Me	34	2	44	20
4	**208**	Ph	Ph	8	8	81	3

Table 6.8: Overnight rearrangement of substrates with catalytic DHPB
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)

The substrates were also treated with NHC **176** (derived from treatment of triazolium salt **175** with KHMDS) and the results are outlined in Table 6.9. The result for *N*(2)-phenyl, *C*(5)-methyl test substrate **199** is once again included for reference (entry 1). Overall, NHC catalysis was superior in terms of both reaction rate and levels of conversion to *C*-carboxyl products compared to the other catalysts tested. The exception was di-phenyl substrate **208** where only 33 % conversion was observed (entry 4). Reaction was extended overnight which significantly improved conversion though the major component was parent pyrazolinone **205** (78 %, entry 4). The other compounds all showed good selectivity for the *C*-carboxylate with the product isolated in moderate yields (45-65 %).



199	R^1 = Me, R^2 = Ph	**200**	**198**	**201**
206	R^1 = Me, R^2 = Me	**211**	**203**	**209**
207	R^1 = Ph, R^2 = Me	**212**	**204**	**214**
208	R^1 = Ph, R^2 = Ph	**213**	**205**	**215**

Entry	Substrate	R^1	R^2	% Ratio				Yield (%)
				O	C	PAR	N	
1	**199**	Me	Ph	0	83	17	0	65 (**200**)
2	**206**	Me	Me	0	70	28	2	45 (**211**)
3	**207**	Ph	Me	1	83	16	0	55 (**212**)
4	**208**	Ph	Ph	67	5	28	9	-
5[a]	**208**	Ph	Ph	13	9	78	0	-

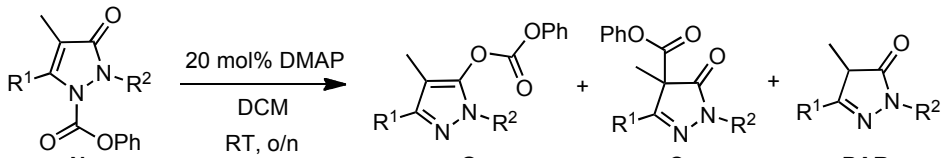
Table 6.9: Rearrangement of substrates with NHC derived from triazolium **176**
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)
a) Overnight reaction

The testing of substrates **206-208** with the various Lewis base catalysts showed product distributions were dependent on reaction time, catalyst and substrate. DMAP was an effective catalyst, giving either predominantly *N*- or *C*-carboxylation depending on the substrate and reaction time. Under DHPB catalysis, high levels of parent pyrazolinone were observed in all cases overnight. The high reactivity of NHC **176** led to significantly shorter reaction times (1 h compared to overnight reaction). *C*-Carboxylation was favoured for all but di-phenyl substrate **208**.

6.3.2 Re-treatment of *N*-carboxylates

The testing of pyrazolyl carbonates **199**, **206-208** with the various Lewis base catalysts resulted in a range of different reactivities and product distributions. To probe the mechanism of these processes, the *N*-carboxylates **201**, **209** and **214** were treated in isolation with DMAP, DHPB and NHC **176**. Despite several attempts, it was not possible to isolate di-phenyl *N*-carboxylate **215**. This was due to the compound only ever being formed in trace quantities during catalysis. (For this reason, the assignment of this component as **215** is from the crude ^{1}H NMR spectrum and should be considered tentative.)

The three isolated *N*-carboxylates were first treated with 20 mol% DMAP and the results are presented in Table 6.10. Only *N*-carboxylate **201** showed any significant conversion (29 %) and this was predominantly to *C*-carboxylate **200** (entry 1). This would imply that *N*-carboxylate **201** represents an intermediate in the conversion of **199** to **200**. For the other compounds, DMAP appears unable to rearrange the *N*-carboxylate to any significant extent (entries 2 and 3).

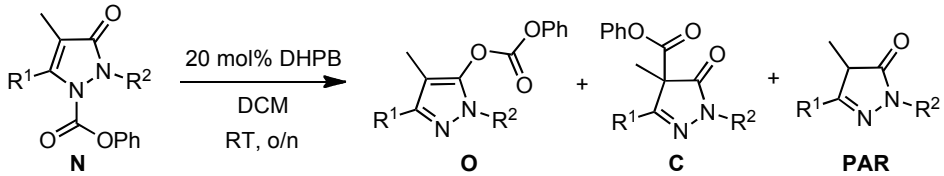


201	R^1 = Me, R^2 = Ph	**199** **200** **198**
209	R^1 = Me, R^2 = Me	**206** **211** **203**
214	R^1 = Ph, R^2 = Me	**207** **212** **204**

Entry	Compound	R^1	R^2	% Ratio			
				O	**C**	**PAR**	**N**
1	**201**	Me	Ph	6	19	4	71
2	**209**	Me	Me	1	0	3	96
3	**214**	Ph	Me	2	4	2	92

Table 6.10: Rearrangement of *N*-carboxylates with DMAP
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)

When the same compounds were treated with DHPB, conversions were significantly higher, particularly with **214** where almost full conversion to pyrazolinone **204** was observed after overnight reaction (entry 3, Table 6.11). In all cases, the pyrazolinone was the major product. These results imply that DHPB is not an effective catalyst at rearranging the carboxyl group to carbon, regardless of the starting position (O or N).

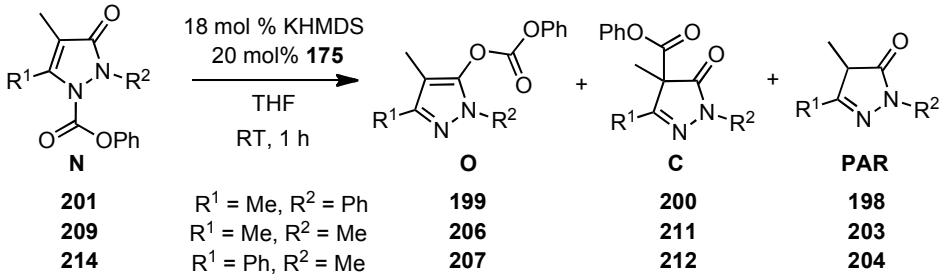


201	R^1 = Me, R^2 = Ph	**199** **200** **198**
209	R^1 = Me, R^2 = Me	**206** **211** **203**
214	R^1 = Ph, R^2 = Me	**207** **212** **204**

Entry	Compound	R^1	R^2	% Ratio			
				O	**C**	**PAR**	**N**
1	**201**	Me	Ph	5	5	29	61
2	**209**	Me	Me	2	0	26	72
3	**214**	Ph	Me	2	0	98	0

Table 6.11: Rearrangement of *N*-carboxylates with DHPB
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)

The final step was treatment with the NHC catalyst derived from triazolium salt **175** (Table 6.12). Despite the short (1 h) reaction time, conversions were generally higher than with the other catalysts tested, indicating the reactivity of the active NHC catalyst. Di-methyl *N*-carboxylate **209** showed the highest conversion and this was predominantly to the *C*-carboxylate product **211** (entry 2). *N*(2)-phenyl, *C*(5)-methyl **201** also favoured *C*-carboxylation (entry 1) while *N*(2)-methyl, *C*(5)-phenyl **214** gave predominantly the parent pyrazolinone (entry 2). This result was unexpected as reaction with *O*-carboxylate **207** had given 83 % *C*-carboxylated product and none of the *N*-carboxylate (see Table 6.9).



Entry	Compound	R^1	R^2	% Ratio			
				O	**C**	**PAR**	**N**
1	**201**	Me	Ph	0	43	21	36
2	**209**	Me	Me	0	63	31	6
3	**214**	Ph	Me	1	14	63	22

Table 6.12: Rearrangement of *N*-carboxylates with NHC derived from triazolium **175**
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)

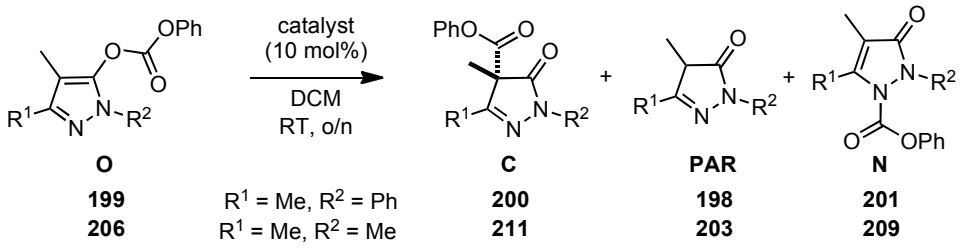
The testing of *N*-carboxylates **201**, **209** and **214** with the various nucleophilic catalysts showed a range of reactivities dependent on both the catalyst and the substrate. DMAP showed some conversion with *N*(2)-phenyl, *C*(5)-methyl carboxylate **201** though generally little rearrangement was observed. The major product upon rearrangement in all cases with DHPB was the respective parent pyrazolinone. With the carbene derived from triazolium salt **175**, dominant *C*-carboxylation appeared to correlate with *C*(5)-methyl substitution; *C*(5)-phenyl substrate **214** giving mainly parent pyrazolinone.

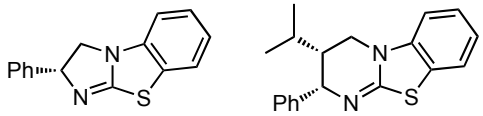
6.4 Asymmetric Steglich rearrangement of pyrazolin-3-ones

6.4.1 Model studies

Attention now turned to the development of an asymmetric protocol in the hopes of producing rearrangement products with high levels of enantiocontrol. At this point, little was known about the reactivity and selectivity of pyrazolinones in such enantioselective processes and so the

results obtained within the group for oxazolyl carbonates were used as a guide.[116,117] Hence, the examination of an enantioselective protocol began with the testing of chiral isothiourea **191**, which was found to catalyse the rearrangement of oxazolyl carbonates with high enantioselectivity (Table 6.13, entry 2).[116] Pyrazolinone **199** was initially chosen as the model substrate and reaction was carried out with 10 mol% catalyst loading. However, despite reasonable 85 % conversion overnight a mixture of products resulted, principal of which was *N*-carboxylate **201** (73 %) and only trace *C*-carboxylate **200** (2 %). An alternative isothiourea scaffold, benzotetramisole **190**, was also investigated but this was found to give just 14 % conversion overnight with only trace product produced (entry 1). As an alternative, di-methyl substrate **206** was tested with catalyst **191** (entry 3). Reactivity was slightly improved (95 %) but no C-carboxylate product was observed, only *N*-carboxylate. In no case was the *C*-carboxylated product isolated.[134]





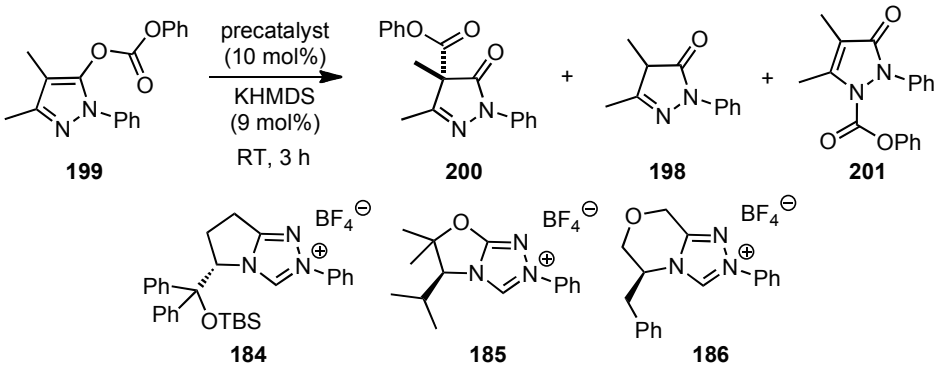
190 **191**

Entry	Substrate	R^1	R^2	Catalyst	% Ratio			
					O	C	PAR	N
1	**199**	Me	Ph	**190**	82	2	12	4
2	**199**	Me	Ph	**191**	15	2	10	73
3	**206**	Me	Me	**191**	5	0	3	93

Table 6.13: Rearrangement of pyrazolyl carbonates **199** and **206** by chiral isothiourea organocatalysts

The poor levels of reactivity and/or product conversion observed in the initial screen of chiral isothioureas led us to investigate alternative modes of catalytic activation. In the racemic organocatalysed reaction it was established that NHCs were superior catalysts to isothioureas, both in terms of reactivity and product distributions. Hence, a selection of chiral triazolium-derived NHC catalysts were tested with substrate **199** and the results are shown in Table 6.14.[135] Reactions were carried out in THF as before, but also in toluene, as toluene had been found to be the optimum solvent for high enantioselectivity in reactions with oxazolyl carbonates.[116]

Reactions were carried out at a reduced catalyst loading of 10 mol% and examined after 3 h. Results with the NHC derived from triazolium salt **184** were disappointing, less than 20 % conversion after 3 h in both solvents was observed with only trace *C*-carboxylate formation, the major component being parent pyrazolinone **198** (entries 1 and 2). More encouraging were the results with the NHC of oxazolidinone-derived triazolium salt **185**, where greater than 90 % conversion was observed in both solvents (entries 3 and 4). More importantly, *C*-carboxylate **(–)-200** was the major component and was isolated in 55 % yield and 46 % ee in THF (entry 3). The yield improved to 74 % when toluene was the solvent, with no change in ee (entry 4). The NHC of triazolium salt **186** also proved to be effective, giving *C*-carboxylate **(–)-200** in 61 % yield and 46 % ee in THF (entry 5). As with **185**, changing solvent to toluene increased the yield, to 71 %, but here also gave a 10 % enhancement of enantioselectivity to 56 % (entry 6). It should be noted that the absolute configuration of the *C*-carboxylated product **(–)-200** has not yet been determined (the minus sign refers to the compounds optical rotation).

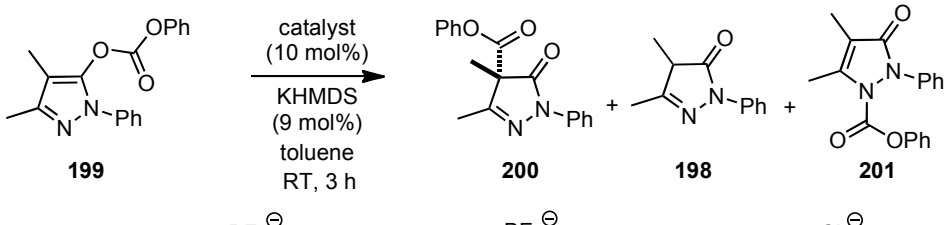


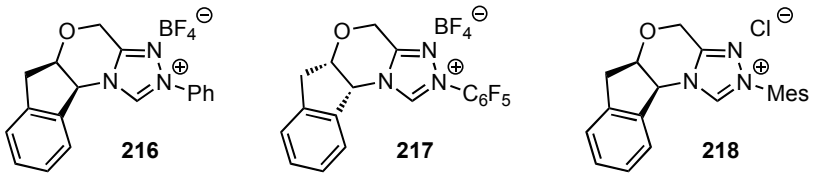
Entry	Precatalyst	Solvent	% Ratio				Yield (%)	% ee[a]
			199	200	198	201		
1	**184**	THF	82	2	12	4	-	-
2		toluene	86	3	10	1	-	-
3	**185**	THF	7	82	10	1	55	–46
4		toluene	2	89	8	1	74	–46
5	**186**	THF	2	87	10	1	61	–46
6		toluene	2	87	11	0	71	–56

Table 6.14: Rearrangement of pyrazolyl carbonate **199** by chiral NHC organocatalysts
a) + and – signs refer to sign of the products optical rotation

As catalyst **186** in toluene gave the best ee and good yield it was decided to focus attention on related morpholinone-derived catalyst architectures in an attempt to further optimise yield and enantioselectivity. In particular, catalysts based on the structure pioneered by Rovis were investigated (Table 6.15). These catalysts have found application in a range of organocatalysed processes, particularly in the catalytic generation of acyl anion equivalents.[136]

A small range of catalysts bearing different protecting groups on nitrogen were then tested, in toluene, against the model substrate. Despite the relatively small structural differences between each catalyst, significant differences in reactivity and enantioselectivity were observed. The NHCs derived from precatalysts **216** and **217** each gave 99 % conversion in 3 h with essentially identical levels of *C*-carboxylate formation (entries 1 and 2). Only in the reaction with precatalyst **217** (entry 2) was the product **(–)-200** isolated and this gave a final yield of 61 % and 61 % ee. For the reaction with precatalyst **216**, the ee was obtained from the crude reaction mixture and was slightly lower at 46 % (entry 1). Surprisingly, despite the absolute configuration of each catalyst being different, they give the same enantiomer as the major product. This could indicate that a markedly different transition state is favoured in each reaction, resulting in an opposite sense of stereoinduction (where each catalysts absolute configuration is the same).[137] In contrast, the NHC derived from precatalyst **218** showed poor reactivity, with an extended reaction time of 18 h necessary to achieve 92 % conversion (entry 3). In addition, the desired *C*-carboxylate **(+)-200** was only a minor component of the crude reaction mixture (30 %), the main product being the parent pyrazolinone **198** (57 %). The enantiomeric excess of **(+)-200** was obtained from the crude reaction mixture and found to be 40 %, the lowest for this series of catalysts.





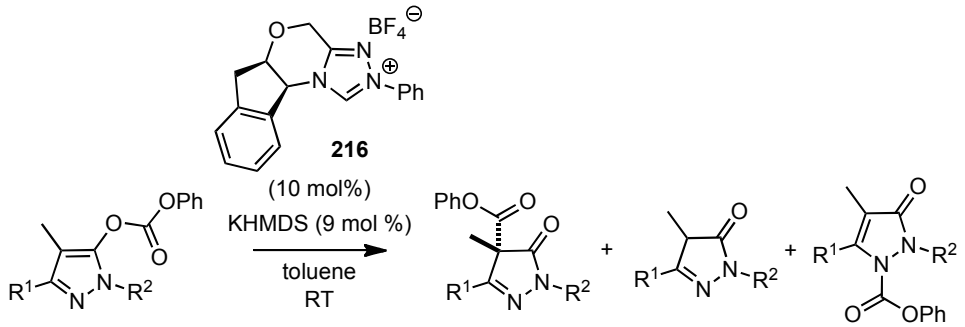
Entry	Precatalyst	% Ratio				200 Yield (%)	% ee[a]
		SM	P	PAR	N		
1	**216**	1	92	6	1	–	–46
2	**217**	1	90	8	1	61	–61
3[b]	**218**	8	30	57	5	–	+40

Table 6.15: Asymmetric Steglich rearrangement of **199**
a) + and – signs refer to sign of the products optical rotation
b) Reaction time of 18 h

6.4.2 Substrate optimisation

It had now been established that chiral triazolium NHCs were active and modestly enantioselective organocatalysts of the Steglich-type rearrangement of pyrazolyl carbonates. We next probed the scope of the reaction by varying the substitution pattern on the pyrazolyl carbonate to observe the effects on reactivity and enantioselectivity. We again focused on substitution at N(2) and C(5) and made use of the same substrates employed in the racemic series (see Section 6.3.1). To further explore the effects of different catalyst structure on the sense of enantioselectivity, each structure was treated with triazolium salts **216** and **217** and the results are presented below.

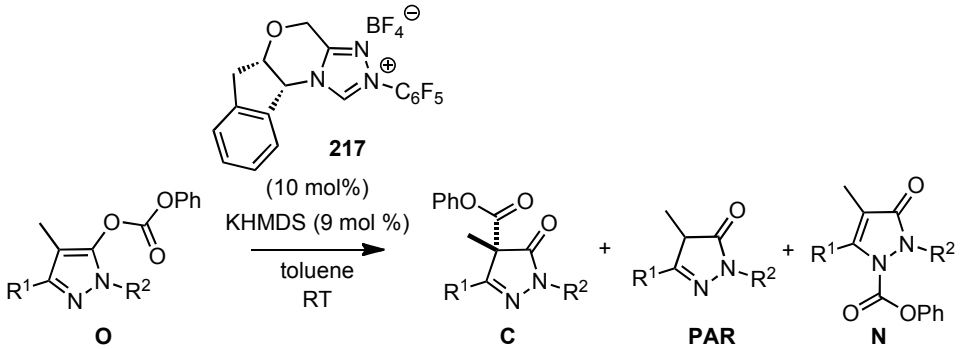
The results of asymmetric catalysis with the *N*-phenyl chiral NHC derived from **216** are outlined in Table 6.16. Reactivity and enantioselectivity correlated with C(5) substitution; *C*(5)-methyl substrates **199** (entry 1) and **206** (entry 2) showed high conversion to *C*-carboxylated products and modest ee's. In contrast, *C*(5)-phenyl substituted substrates **207** (entry 3) and **208** (entry 4) required longer reaction times and gave predominantly parent pyrazolinone. *C*-carboxylates were isolated in both low yields and low enantioselectivities.



Entry	Substrate	R^1	R^2	Time (h)	% Ratio				*C*-carboxylate yield (%)	% ee
					O	C	PAR	N		
1	**199**	Me	Ph	3	1	92	6	1	–	46
2	**206**	Me	Me	3	0	68	18	14	49	45
3	**207**	Ph	Me	18	5	28	64	3	10	10
4	**208**	Ph	Ph	96	1	8	90	1	4	<5

Table 6.16: Rearrangement of substrates with NHC derived from *N*-phenyl triazolium **216**
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)

With *N*-C_6F_5 triazolium **217**, di-methyl **206** was again a good substrate in terms of both reactivity and enantioselectivity and gave an ee of 86 % (Table 6.17, entry 2). This level of enantioselectivity is significantly higher than the best results found with oxazolyl carbonates and chiral carbenes where the highest ee achieved was 50 % despite extensive optimisation.[116] *N*(2)-methyl, *C*(5)-phenyl substrate **207** again showed low reactivity, gave a mixture of products and low ee of the desired *C*-carboxylate (6 % ee, entry 3). However, di-phenyl substrate **208** showed much better reactivity than with the previous catalyst, giving *C*-carboxylate in 48 % yield, though with low enantioselectivity (entry 4). Finally, with the exception of di-phenyl substrate **208**, *N*-C_6F_5 triazolium **217** again gave the same absolute configuration in the *C*-carboxylated products as *N*-phenyl **216**.



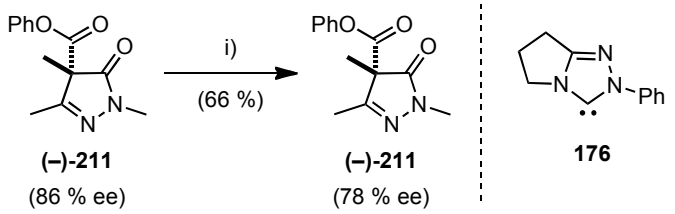
Entry	Substrate	R^1	R^2	Time (h)	% Ratio				*C*-carboxylate yield (%)	% ee
					O	C	PAR	N		
1	**199**	Me	Ph	3	1	90	8	1	61	61
2	**206**	Me	Me	3	0	72	15	13	61	86
3	**207**	Ph	Me	18	25	22	47	6	7	6
4	**208**	Ph	Ph	18	0	79	21	0	48	-20

Table 6.17: Rearrangement of substrates with NHC derived from *N*-C_6F_5 triazolium **217**
(**O** = *O*-carboxylate substrate, **C** = *C*-carboxylate, **PAR** = parent compound, **N** = *N*-carboxylate)

6.4.3 Preliminary mechanistic investigations

As a preliminary step in the delineation of the reaction mechanism, the enantioenriched *C*-carboxylate **(–)-211** (86 % ee) was treated with achiral NHC **176** (Scheme 6.6). After 3 h, **(–)-211** was isolated in 66 % yield and a slightly reduced ee of 78 %. This was in contrast to

analogous reactions with oxazolyl carbonates in which the ee remained unchanged after treatment with an achiral NHC.[116]



Scheme 6.6: *Reagents and conditions*: i) **175** (20 mol%), KHMDS (18 mol%), toluene, 3 h, rt.

This drop in enantioselectivity implies that carbon-carbon bond formation is a reversible process under catalysis with racemic NHC **176** (Figure 6.16). Crossover experiments with oxazolyl carbonates have shown that the first step, formation of enolate **B** and carboxylate **C**, is also reversible although such experiments have not yet been carried out with pyrazolyl carbonates. In addition, the reversibility of carbon-carbon bond formation with chiral NHCs or the other Lewis base catalysts examined has not yet been established.

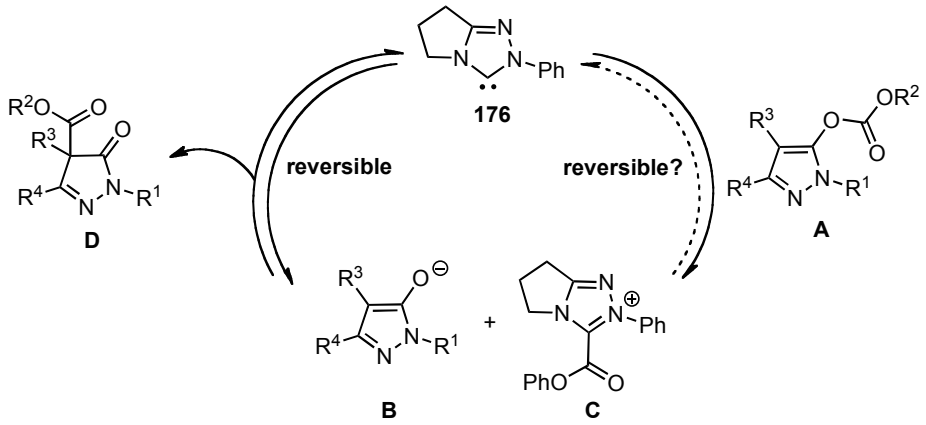


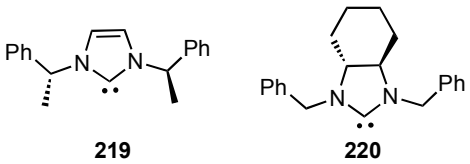
Figure 6.16: Updated catalytic cycle under NHC **176** catalysis

6.5 Summary

In preliminary studies, pyrazolin-3-ones were found to be suitable substrates for the organocatalysed Steglich rearrangement. NHCs were generally found to be superior to DMAP and isothioureas in terms of both reactivity and regioselectivity for *C*-carboxylates over *N*-carboxylates or carbonate loss to give parent pyrazolinones. Treatment of *N*-carboxylates **201**, **209** and **214** showed a similar trend with NHCs again showing the greatest reactivity and *C*-carboxylate selectivity. In the asymmetric reaction, chiral NHCs based on a morpholinone skeleton were most enantioselective, particularly with methyl substitution at N(2) and C(5). Re-treatment of enantioenriched di-methyl *C*-carboxylate **(–)-211** with an achiral NHC led to a small loss of ee, indicating the reversible nature of the key C-C bond-forming step.

6.6 Future work

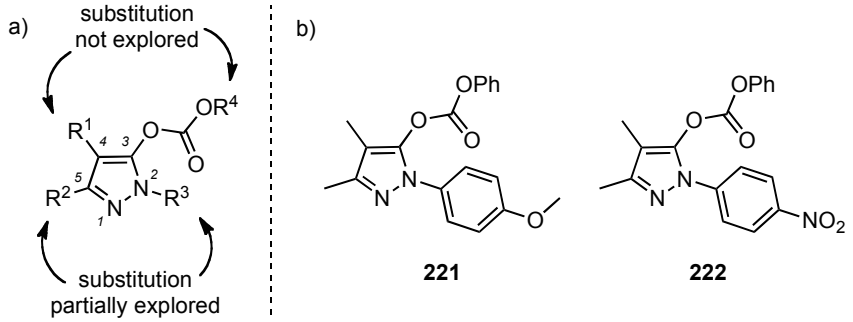
Studies with pyrazolyl carbonates have already shown that rearrangement products can be formed with good yields and high ee. However, there remains substantial scope for further optimisation of reaction conditions, for example the use of low temperatures to enhance enantioselectivity. NHC catalyst concentration greatly influenced product distribution with related furanyl carbonates but has not yet been investigated with pyrazolyl carbonates. Further exploration of the catalyst structure might also be instructive with the use of imidazolium and imidazolinium catalysts, such as **219** and **220** respectively, yet to be explored (Figure 6.17).



219 **220**

Figure 6.17: Example imidazolium catalyst **219** and imidazolinium **220**

Establishing optimum reaction conditions would then allow a full exploration of substrate scope. Preliminary studies have focused on the substitution at the N(2) and C(5) positions (Figure 6.18a)) but variation of the carbonate or the key C(4)-position has not been explored. Although some investigation of N(2) and C(5) substitution has taken place, this has focused exclusively on methyl and phenyl substituted pyrazolyl carbonates. While this has been fruitful, it is not possible from current results to attribute differences in product distributions/ enantioselectivities to either electronic or steric factors (or a combination of the two). Expansion into substituted aryl pyrazolinones e.g. **221** and **222**, would allow electronic factors to be examined independently (Figure 6.18b)).



221 **222**

Figure 6.18: Substrates to probe effect of changing electronics on product distributions/ enantioselectivities

In terms of enantioselectivity, it is now established that methyl substitution at N(2) and particularly C(5), rather than phenyl, gives higher product yields and enantioselectivities in reactions with chiral NHCs. However, the effect of other substitution at these, and other

positions, have not been explored. In addition, a priority remains determination of the absolute configuration of *C*-carboxylated products as a key step in the rationalisation of observed results and construction of a transition state model. Obtaining the X-ray crystal structure of a suitable enantioenriched product would be the most straightforward method for such a determination.

Chapter 7: Experimental

7.1 General experimental

All reactions involving moisture sensitive reagents were performed under an atmosphere of argon or nitrogen using standard vacuum line techniques and with freshly distilled solvents. All glassware was flame dried and allowed to cool under vacuum. Temperatures of 0 ºC were obtained using an ice/water bath and of –78 ºC were obtained using a dry ice/acetone bath. Room temperature refers to 20–25 ºC. For compounds synthesised by multiple routes, only experimental details for the highest yielding route are included.

All dried and purified solvents were obtained from a solvent purification system (MBraun, SPS-800) except for dry *N,N′*-dimethylformamide (DMF) which was purchased directly from Aldrich. Petrol refers to the fraction of petroleum ether boiling between 40 ºC and 60 ºC, dioxane refers to 1,4-dioxane, pH 7 phosphate buffer refers to a solution of sodium dihydrogen phosphate and di-sodium hydrogen orthophosphate and brine refers to a saturated aqueous solution of sodium chloride. Cyclopentadiene was obtained by cracking of the dimer at 170 ºC, after drying over $MgSO_4$, and stored in the freezer. Catalytic runs for which isolated yields were obtained were carried out with aldehydes purified according to the guidelines of Perrin and Chai.[138] All other reagents were used directly as supplied without further purification.

Flash column chromatography was carried out according to the method of Still[139] with silica gel 60 (0.043-0.060 mm) (Merck) in the solvent system stated. A Biotage Isolera flash purification system was also used for chromatography where stated. Analytical thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60 F_{254}). TLCs were visualised either by UV fluorescence (254 nm), or by staining with basic $KMnO_4$ solution.

Optical rotations were determined using a PerkinElmer Model 341 Polarimeter, at 20.0 ºC using a Na/Hal lamp tuned to 589 nm and with a 100 mm path length.

Melting points were recorded on an Electrothermal apparatus and are uncorrected. Microanalyses were carried out on a Carlo Erba CHNS analyser. Infrared spectra were recorded on a Perkin-Elmer Spectrum GX FT-IR Spectrometer and analysed either as thin films between NaCl plates (thin film) or KBr discs (KBr disc) as stated. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and only structurally significant peaks are quoted.

^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz ^{1}H, 75 MHz ^{13}C, 282 MHz ^{19}F), a Bruker Avance 400 (400 MHz ^{1}H, 100 MHz ^{13}C, 376 MHz ^{19}F) or a Bruker Avance 500 (500 MHz ^{1}H, 125 MHz ^{13}C, 470 MHz ^{19}F) spectrometer in the deuterated solvent stated. ^{13}C NMR spectra were recorded with proton decoupling. ^{15}N NMR spectra were acquired indirectly by ^{1}H, ^{15}N-HMBC experiments on a Bruker Avance 500 equipped by a 5 mm inverse tuneable double resonance probe. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to residual solvent peaks. Coupling constants, *J*, are quoted in Hz. The abbreviations s, d, dd, t, dt, td, tt, q, dq, quin, sext, desxt, sept, dsept and m denote singlet, doublet, doublet of doublets, triplet, doublet of triplets, triplet of doublets, triplet of triplets, quartet, doublet of quartets, quintet, sextet, doublet of sextets, doublet of septets and multiplet respectively. *app* stands for apparent and *br* for broad. The abbreviation Ar is used to denote aromatic. For compounds displaying rotamers or tautomers in ^{1}H NMR spectroscopy, the integral ratio of the two species is given with the more abundant designated A and the less abundant designated B.

Mass spectrometric (*m/z*) data was acquired by electrospray ionisation (ESI) or chemical ionisation (CI), either at the University of St Andrews Mass Spectrometry facility or at the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS was carried out on a Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, CI MS was carried out on a Micromass Quattro II spectrometer. High resolution ESI was carried out on a Finnigan MAT 900 XLT; a Thermofisher LTQ Orbitrap XL spectrometer was used to obtain high resolution ESI MS for accurate mass determination but also provided fragmentation data for the characterisation of samples. Values are quoted as a ratio of mass to charge in Daltons.

Chiral HPLC was performed on Gilson apparatus, using a ChiralPak AD-H, AS-H, OD-H, or OJ-H or IB silica column, 0.46 cm ϕ x 25 cm, using hexane and isopropanol as eluents.

^{15}N NMR calculations were carried out by Tomas Lebl using Spartan '08 modelling program. Calculations were carried out at the B3LYP level of theory using the 6-31G* basis set.

7.2 General experimental procedures

General procedure A: O-*functionalisation of* (*RS*)-*tert-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate* ***72*** *with triethylamine*

To a solution of (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (1 eq) in dichloromethane (0.5 M) was added triethylamine (1.1 eq). The resulting suspension was then cooled to 0 ≡C and the appropriate chloride or anhydride (1.05 eq) added. The mixture was allowed to warm to rt overnight. The reaction was quenched with water and extracted three times with dichloromethane. The combined organic layers were washed with 0.1 M aqueous hydrochloric acid, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General procedure B: N*(2)-alkylation of Boc-protected pyrazolidin-3-one with sodium hydride*

A solution of the appropriate Boc-protected pyrazolidin-3-one (1 eq) in dichloromethane (0.5 M) was cooled to −78 ≡C and sodium hydride (60 % dispersion in mineral oil, 1.1 eq) added. The resulting suspension was stirred for 10 min before addition of the appropriate chloride or anhydride (1.05 eq). The mixture was allowed to warm to rt overnight. The reaction was quenched with water and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General procedure C: *screening of aldehyde substrates under racemic catalysis*

To a suspension of catalyst (20 mol %, 0.189 mmol) in methanol (1 mL) was added triflic acid (17.0 μl, 0.189 mmol). After 2 min of stirring, the appropriate aldehyde (0.950 mmol) was added, followed by a further 15 min of stirring. Cyclopentadiene (188 mg, 2.80 mmol) was then added and the resulting mixture left to stir at rt. Reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated *in vacuo* then hydrolysed in a chloroform (2 mL), water (1 mL), trifluoroacetic acid (1 mL) mixture for 2 h. Saturated sodium hydrogen carbonate solution (20 mL) was then added and the resulting biphasic mixture extracted with chloroform (2 x 20 mL). The combined organic layer were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General procedure D: *substrate screening with chiral iminium ion catalysts*

The appropriate catalyst (X mol%) was suspended in a solution of triflic acid in methanol (X mol%). After 2 min of stirring, the appropriate aldehyde (0.950 mmol) was added, followed

by a further 15 min of stirring. The appropriate diene (2.80 mmol) was then added and the resulting mixture left to stir at rt. Reaction was monitored by TLC and, upon completion, worked up as described in general procedure C.

Procedure E: *Amide coupling of pyrazolidin-3-one to a chiral acid using 1 equivalent of N-(3-dimelhylaminopropyl)-N'-ethylcarbodiimide hydrochloride and 1 equivalent of 1-hydroxybenzotriazole*

N-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1 eq), 1-hydroxybenzotriazole (1 eq) and the appropriate chiral acid (1 eq) were combined in either THF or DMF (0.1 M) and stirred at room temperature for 15 minutes. The appropriate pyrazolidin-3-one (1 eq) was then added and the resultant solution stirred at rt overnight. The reaction mixture was then concentrated *in vacuo* and the resultant residue taken up in dichloromethane, washed twice with 0.1 M hydrochloric acid solution followed by single washes with saturated sodium bicarbonate solution and brine before being dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General procedure F: *Derivatisation of an aldehyde to the benzoyl ester*

To a solution of the appropriate aldehyde (1 eq) in methanol (0.15 M) was added sodium borohydride (3 eq) and the resulting suspension stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* before being suspended in a mixture of water and brine and extracted with dichloromethane (x 2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting material was dissolved in dichloromethane (0. 15 M) and treated with triethylamine (1.5 eq), DMAP (1 eq) and benzoyl chloride (1.2 eq) then stirred at room temperature overnight. Reaction was quenched with saturated ammonium chloride solution and extracted with diethyl ether (x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.[48]

Procedure G: *Condensation of monosubstituted hydrazine with β-ketoester to give 5-pyrazolin-3-ones*

To a solution of the required β-ketoester (1 eq) in absolute ethanol (1-1.4 M) was added the required monosubstituted hydrazine (1.1 eq) dropwise and the resulting solution stirred at reflux overnight. The suspension was then concentrated *in vacuo*.

Procedure H: *O-Carboxylation of 5-pyrazolin-3-ones*

Based upon a procedure by Fu and co-workers,[95] triethylamine (1.1 eq) was added to a stirred solution of the required 5-pyrazolin-3-one (1 eq) in THF (0.5-0.8 M) at 0 ºC, followed by addition of the required chloroformate (1.05 eq) after 15 min. The mixture was stirred at ambient temperature overnight. The resulting solution was poured into water and the aqueous phase extracted with diethyl ether (x 3). The combined organic layers were washed with 1 M hydrochloric acid solution, sodium hydrogen carbonate solution, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Procedure I: *Treatment of a pyrazolyl carbonate or N-carboxylated pyrazolin-3-one with DMAP or DHPB*

To a solution of the appropriate pyrazolyl carbonate or *N*-carboxylated pyrazolin-3-one (1 eq) in dichloromethane (0.1 M) was added either DMAP (20 mol%) or DHPB (20 mol%), as appropriate, and the mixture left to stir at rt. Reaction was quenched by the addition of 0.1 M hydrochloric acid solution and extracted with dichloromethane (x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo* and analysed by ^{1}H NMR spectroscopy. Where applicable, this crude mixture was re-suspended in dichloromethane and treated with conditions identical to those described above.

Procedure J: *Treatment of a pyrazolyl carbonate or N-carboxylated pyrazolin-3-one with achiral carbene **176***

To a mixture of triazolium salt **175** (20 mol%) and the appropriate pyrazolyl carbonate or *N*-carboxylated pyrazolin-3-one (1 eq) in THF (0.1 M), as appropriate, was added KHMDS (0.5 M solution in toluene, 18 mol%) and the mixture left to stir at rt. Reaction was quenched by the addition of 0.1 M hydrochloric acid solution and extracted with dichloromethane (x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo* and analysed by ^{1}H NMR spectroscopy.

Procedure K: *Treatment of a pyrazolyl carbonate with a chiral carbene*

To a mixture of the required triazolium salt (10 mol%) and the appropriate pyrazolyl carbonate (1 eq) in THF or toluene (0.2 M) was added KHMDS (0.5 M solution in toluene, 9 mol%) and the mixture left to stir at rt. Reaction was quenched by the addition of 0.1 M hydrochloric acid solution and extracted with dichloromethane (x 3). The combined organic layers were washed

with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo* and analysed by ^1H NMR spectroscopy.

Screening of racemic catalysts for $t^{1/2}$ values

To a suspension of catalyst (20 mol %, 0.378 mmol) in methanol (2 mL) was added triflic acid (35.0 μl, 0.378 mmol). After 2 min of stirring, (*E*)-cinnamaldehyde **37** (0.240 mL, 1.89 mmol) was added, followed by a further 5 min of stirring. Cyclopentadiene (370 mg, 5.60 mmol) was then added and the resulting mixture left to stir at rt. The reaction was monitored by taking samples of the reaction mixture (0.05 mL) which were concentrated *in vacuo* then hydrolysed in a chloroform (1 mL), water (0.5 mL), trifluoroacetic acid (0.5 mL) mixture for 2 h. Saturated sodium hydrogen carbonate solution (10 mL) was then added and the resulting biphasic mixture extracted with chloroform (2 x 10 mL). The combined organic layer were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. ^1H NMR spectroscopy of the crude reaction mixture was used to establish the conversion to the products and *exo*:*endo* ratios through the integration of aldehyde peaks at: δ_H 9.93 (***exo*-38**), 9.64 ((*E*)-cinnamaldehyde **37**) and 9.60 (***endo*-38**) which were in accordance with previously reported literature values.[63,64]

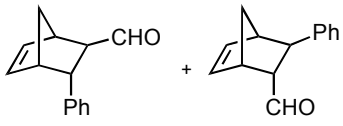
Screening of chiral iminium ion catalysts

(*E*)-Cinnamaldehyde **37** (0.120 mL, 0.950 mmol) and the appropriate chiral catalyst (20 mol %, 0.189 mmol) were combined according to general procedure C. The crude material was then purified by column chromatography, eluting with 5 % diethyl ether in petrol to yield ***exo*-38** and ***endo*-38**, with spectroscopic data in accordance with the literature.[64] Enantiomeric excesses were determined by acetalisation with (+)-(*R,R*)-hydrobenzoin and ^1H NMR analysis: (500 MHz, C_6D_6) *exo* isomers δ 5.74 (d, *J* 4.8, C*H*O_2, 2*R*) and 5.72 (d, *J* 5.8, C*H*O_2, 2*S*), *endo* isomers δ 5.37 (d, *J* 8.1, C*H*O_2, 2*R*) and 5.33 (d, *J* 8.2, C*H*O_2, 2*S*).

7.3 Experimental procedures

7.3.1 Diels-Alder adducts described in Tables 2.3, 5.4 and 5.6

exo-(1*RS*,2*RS*,3*RS*,4*SR*)-3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde _exo_-38 and _endo_-(1*SR*,2*RS*,3*RS*,4*RS*)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde _endo_-38 (Table 2.3, entry 1)



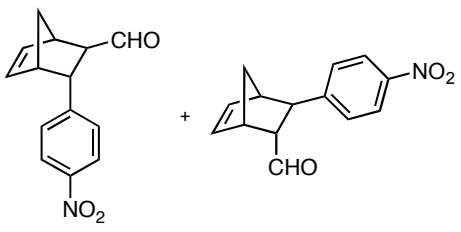
***exo*-38** ***endo*-38**

(*E*)-Cinnamaldehyde **37** (0.120 mL, 0.950 mmol) and catalyst **114** (56 mg, 0.190 mmol) were combined according to general procedure C. The crude material was then purified by column chromatography, eluting with 5 % diethyl ether in petrol to yield the title compounds as a 62:38 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (168 mg, 89 %).[63,64]

Compound exo-38: δ_H (300 MHz, $CDCl_3$) 9.93 (1H, d, *J* 2.1, C*H*O), 7.34–7.13 (5H, m, Ar*H*), 6.34 (1H, dd, *J* 5.8, 3.6, CH_A=CH_B), 6.08 (1H, dd, *J* 5.8, 3.3, CH_A=CH_B), 3.73 (1H, dd, *J* 5.2, 3.4, C*H*Ph), 3.24–3.21 (2H, m, C*H*CH_2), 2.60 (1H, app dt, *J* 5.2, 2.1, C*H*CHO) and 1.62–1.53 (2H, m, CH_2).

Compound endo-38: δ_H (300 MHz, $CDCl_3$) 9.60 (1H, d, *J* 2.2, C*H*O), 7.34–7.13 (5H, m, Ar*H*), 6.42 (1H, dd, *J* 5.7, 3.2, CH_A=CH_B), 6.18 (1H, dd, *J* 5.7, 2.8, CH_A=CH_B), 3.36–3.32 (1H, m, C*H*CH_2), 3.14–3.12 (1H, m, C*H*CH_2), 3.09 (1H, dd, *J* 4.8, 1.5, C*H*Ph), 2.98 (1H, ddd, *J* 4.8, 3.4, 2.2, C*H*CHO), 1.84–1.79 (1H, m, CH_AH_B) and 1.65–1.63 (1H, m, CH_AH_B).

exo-(1*RS*,2*RS*,3*RS*,4*SR*)-3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and _endo_-(1*SR*,2*RS*,3*RS*,4*RS*)-3-(4-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 2.3, entry 2)



exo ***endo***

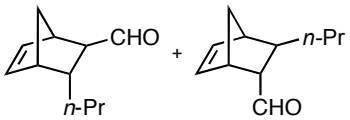
4-Nitrocinnamaldehyde (168 mg, predominantly (*E*)-, 0.950 mmol) and catalyst **114** (56 mg, 0.190 mmol) were combined according to general procedure C. The crude material was then

purified by column chromatography, eluting with 10 % diethyl ether in petrol to yield the product as a 65:35 mixture of diastereoisomers with spectroscopic data in accordance with the literature (169 mg, 73 %).[67]

exo: δ_H (300 MHz, $CDCl_3$) 9.92 (1H, d, *J* 1.7, C*H*O), 8.13–8.08 (2H, m, Ar*H*), 7.32–7.27 (2H, m, Ar*H*), 6.41 (1H, dd, *J* 5.7, 3.2, CH_A=CH_B), 6.05 (1H, dd, *J* 5.7, 2.8, CH_A=CH_B), 3.88 (1H, dd, *J* 5.0, 3.5, C*H*Ar), 3.36–3.32 (1H, m, C*H*CH_2), 3.27–3.33 (1H, m, C*H*CH_2), 2.62 (1H, br d, *J* 5.0, C*H*CHO) and 1.62–1.60 (2H, m, CH_2).

endo: δ_H (300 MHz, $CDCl_3$) 9.64 (1H, d, *J* 1.7, C*H*O), 8.19–8.14 (2H, m, Ar*H*), 7.45–7.40 (2H, m, Ar*H*), 6.44 (1H, dd, *J* 5.9, 3.6, CH_A=CH_B), 6.20 (1H, dd, *J* 5.7, 2.8, CH_A=CH_B), 3.45–3.41 (1H, m, C*H*CH_2), 3.22–3.18 (2H, m, C*H*Ar and C*H*CH_2), 2.95 (1H, ddd, *J* 5.0, 3.5, 1.7, C*H*CHO) and 1.78–1.68 (2H, m, CH_2).

exo-(1*RS*,2*RS*,3*RS*,4*SR*)-3-Propylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and _endo_-(1*SR*,2*RS*,3*RS*,4*RS*)-3-propylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 2.3, entry 3)



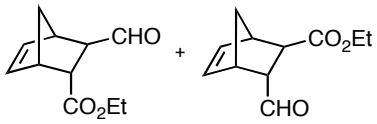
exo ***endo***

(*E*)-2-Hexen-1-al (0.110 mL, 0.950 mmol) and catalyst **114** (56 mg, 0.190 mmol) were combined according to general procedure C. The crude material was then purified by column chromatography, eluting with 2.5 % ethyl acetate in petrol to yield the product as a 58:42 mixture of diastereoisomers with spectroscopic data in accordance with the literature (117 mg, 75 %).[1,140]

exo: δ_H (300 MHz, $CDCl_3$) 9.78 (1H, d, *J* 2.8, C*H*O), 6.21 (1H, dd, *J* 5.7, 3.1, CH_A=CH_B), 6.13 (1H, dd, *J* 5.7, 2.9, CH_A=CH_B), 3.03–2.98 (1H, m, C*H*CH2), 2.89–2.85 (1H, m, C*H*CH2), 2.28 (1H, tdd, *J* 7.6, 4.7, 3.1 C*H*CH_2CH_2), 1.76 (1H, ddd, *J* 4.7, 2.8, 1.7, C*H*CHO), 1.77–1.06 (6H, m, CHCH_2CH & CH_2CH_2) and 0.88 (3H, t, *J* 7.2, CH_3).

endo: δ_H 9.37 (1H, d, *J* 3.4, C*H*O), 6.27 (1H, dd, *J* 5.7, 3.2, CH_A=CH_B), 6.06 (1H, dd, *J* 5.7, 2.8, CH_A=CH_B), 3.14–3.10 (1H, m, C*H*CH2), 2.68–2.64 (1H, m, C*H*CH2), 2.38 (1H, dt, *J* 4.4, 3.4, C*H*CHO), 1.72 (1H, m, C*H*CH_2CH_2), 1.77–1.06 (6H, m, CHCH_2CH & CH_2CH_2) and 0.88 (3H, t, *J* 7.2, CH_3).

exo-(1*RS*,2*RS*,3*RS*,4*SR*)-Ethyl 3-formylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and _endo_-(1*SR*,2*RS*,3*RS*,4*RS*)-ethyl 3-formylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 2.3, entry 4)



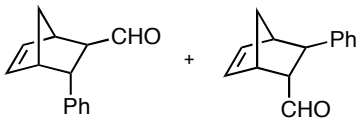
exo ***endo***

Ethyl (*E*)-4-oxo-2-butenoate (0.120 mL, 0.950 mmol) and catalyst **114** (56 mg, 0.190 mmol) were combined according to general procedure C. The crude material was then purified by column chromatography, eluting with 15 % diethyl ether in petrol to yield the product as a 50:50 mixture of diastereoisomers with spectroscopic data in accordance with the literature (147 mg, 80 %).[50,141]

exo: δ_H (300 MHz, $CDCl_3$) 9.84 (1H, d, *J* 0.9, C*H*O), 6.30 (1H, dd, *J* 5.6, 3.2, CH_A=CH_B), 6.13 (1H, dd, *J* 5.6, 2.8, CH_A=CH_B), 4.11 (2H, d, *J* 7.1, OCH_2), 3.42 (1H, dd, *J* 4.4, 3.7, C*H*CO_2), 3.31–3.27 (1H, m, C*H*CH_2), 3.22–3.18 (1H, m, C*H*CH_2), 2.83–2.81 (1H, m, C*H*CHO), 1.47–1.42 (1H, m, CH_ACH_B), 1.36–1.11 (1H, m, CH_ACH_B) and 1.24 (3H, t, *J* 7.1, CH_3).

endo: δ_H 9.55 (1H, d, *J* 1.2, C*H*O), 6.26 (1H, dd, *J* 5.7, 3.3, CH_A=CH_B), 6.09 (1H, dd, *J* 5.7, 2.6, CH_A=CH_B), 4.16 (2H, q, *J* 7.1, OCH_2), 3.39–3.33 (2H, m, C*H*CO_2 and C*H*CH_2), 3.22–3.18 (1H, m, C*H*CH_2), 2.70 (1H, ddd, *J* 4.3, 1.2, 0.5, C*H*CHO), 1.69–1.65 (1H, m, CH_ACH_B), 1.53–1.48 (1H, m, CH_ACH_B) and 1.27 (3H, t, *J* 7.1, CH_3).

exo-(1*R*,2*R*,3*R*,4*S*)-3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde _exo_-(2*R*)-38 and _endo_-(1*S*,2*R*,3*R*,4*R*)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde _endo_-(2*R*)-38 (Table 5.4, entry 1)

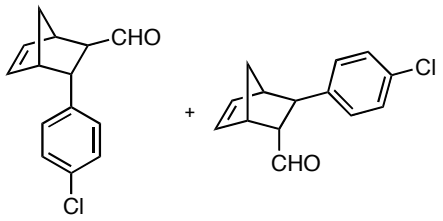


***exo*-(2*R*)-38** ***endo*-(2*R*)-38**

(*E*)-Cinnamaldehyde **37** (0.120 mL, 0.950 mmol), triflic acid (0.190 M solution in methanol, 0.5 mL, 95.0 μmol), catalyst **(5*R*)-163** (10 mol%, 37.0 mg, 95.0 μmol) and cyclopentadiene (188 mg, 2.80 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 5 % diethyl ether in petrol to yield the title compounds as a 35:65 mixture of diastereoisomers, with spectroscopic data identical to that of the racemate (159 mg, 84 %).

Enantiomeric excess was determined by acetalisation with (+)-(*R,R*)-hydrobenzoin and ^{1}H NMR analysis:[67] (500 MHz, C_6D_6) *exo* isomers **δ** 5.74 (d, *J* 4.8, C*H*O$_2$, 2*R*) and 5.72 (d, *J* 5.8, C*H*O$_2$, 2*S*), *endo* isomers **δ** 5.37 (d, *J* 8.1, C*H*O$_2$, 2*R*) and 5.33 (d, *J* 8.2, C*H*O$_2$, 2*S*).

exo-(1*R*,2*R*,3*R*,4*S*)-3-(4-Chlorophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and _endo_-(1*S*,2*R*,3*R*,4*R*)-3-(4-chlorophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5.4, entry 3)



***exo*-(2*R*)** ***endo*-(2*R*)**

Following the method of Baldwin *et al.*,[142] 4-chlorobenzaldehyde (1.00 g, 7.11 mmol) in toluene (7 mL) was heated to 80 ºC and (triphenylphosphoranylidene) acetaldehyde (2.16 g, 7.11 mmol) was added portionwise and the resulting mixture stirred at 80 ºC for 5 h. The solvent was the removed *in vacuo* ((*E*):(*Z*) 77:23) and the crude material purified by column chromatography, eluting with 25 % diethyl ether in petrol, followed by recrystallisation from petrol and a minimum of diethyl ether to give (*E*)-4-chlorocinnamaldehyde as a yellow solid, with spectroscopic data in accordance with the literature (330 mg, 26 %).[143]

***δ*$_H$** (300 MHz, $CDCl_3$) 9.71 (1H, d, *J* 7.6, C*H*O), 7.53–7.49 (2H, m, Ar*H*), 7.43 (1H, d, *J* 16.0, C*H*CHCHO), 7.41–7.39 (2H, m, Ar*H*) and 6.69 (1H, dd, *J* 16.0, 7.6, C*H*CHO).

(*E*)-4-Chlorocinnamaldehyde (172 mg, 0.950 mmol), triflic acid (0.190 M solution in methanol, 0.5 mL, 95.0 μmol), catalyst **(5*R*)-163** (10 mol%, 37.0 mg, 95.0 μmol) and cyclopentadiene (188 mg, 2.80 mmol) were combined at 5 ºC according to general procedure D. The crude material was then purified by column chromatography, eluting with 10 % diethyl ether in petrol to yield the title compounds as a 34:66 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (187 mg, 86 %).[70]

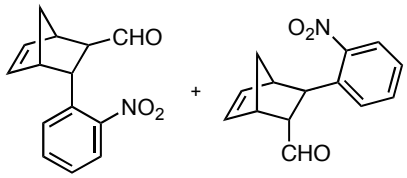
***exo*-(2*R*)**: ***δ*$_H$** (300 MHz, $CDCl_3$) 9.90 (1H, d, *J* 1.8, C*H*O), 7.22–7.18 (2H, m, Ar*H*), 7.08–7.05 (2H, m, Ar*H*), 6.35 (1H, dd, *J* 5.5, 3.1, CH_A=CH$_B$), 6.05 (1H, dd, *J* 5.5, 2.9, CH$_A$=CH_B), 3.70 (1H, dd, *J* 5.0, 3.6, C*H*Ar), 3.25–3.21 (1H, m, C*H*CH$_2$), 3.19–3.16 (1H, m, C*H*CH$_2$), 2.54 (1H, app dt, *J* 5.0, 1.8, C*H*CHO) and 1.59–1.56 (2H, m, CH_2).

***endo*-(2*R*)**: ***δ*$_H$** (300 MHz, $CDCl_3$) 9.59 (1H, d, *J* 2.0, C*H*O), 7.29–7.25 (2H, m, Ar*H*), 7.22–7.18 (2H, m, Ar*H*), 6.41 (1H, dd, *J* 5.6, 3.2, CH_A=CH$_B$), 6.17 (1H, dd, *J* 5.6, 2.8, CH$_A$=CH_B),

3.38–3.32 (1H, m, C*H*CH_2), 3.11–3.08 (1H, m, C*H*CH_2), 3.08–3.03 (1H, m, C*H*Ar), 2.91 (1H, ddd, *J* 5.1, 3.3, 2.0, C*H*CHO), 1.76 (1H, app dt, *J* 8.7, 1.6, CH_AH_B) and 1.65–1.60 (1H, m, CH_AH_B).

Enantiomeric excess was determined by acetalisation with (+)-(*R,R*)-hydrobenzoin and ^{1}H NMR analysis:[67] (500 MHz, C_6D_6) *exo* isomers **δ** 5.66 (d, *J* 5.0, C*H*O_2, 2*R*) and 5.64 (d, *J* 5.9, C*H*O_2, 2*S*), *endo* isomers **δ** 5.31 (d, *J* 8.2, C*H*O_2, 2*R*) and 5.25 (d, *J* 8.3, C*H*O_2, 2*S*).

exo-(1*R*,2*R*,3*R*,4*S*)-3-(2-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and _endo_-(1*S*,2*R*,3*R*,4*R*)-3-(2-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5.4, entry 5)



***exo*-(2*R*)** ***endo*-(2*R*)**

(*E*)-2-Nitrocinnamaldehyde (168 mg, 0.950 mmol), triflic acid (0.190 M solution in methanol, 0.5 mL, 95.0 μmol), catalyst **(5*R*)-163** (10 mol%, 37.0 mg, 95.0 μmol) and cyclopentadiene (188 mg, 2.80 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 15 % ethyl acetate in petrol to yield the title compounds as a 17:83 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (195 mg, 85 %).[67]

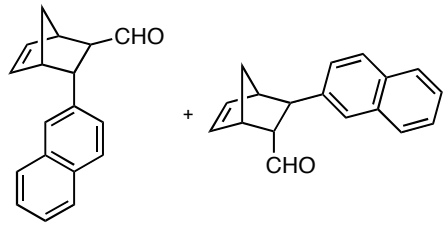
***exo*-(2*R*)**: δ_H (300 MHz, $CDCl_3$) 9.80 (1H, d, *J* 2.1, C*H*O), 7.72 (1H, dd, *J* 8.0, 1.4, Ar*H*), 7.46–7.30 (2H, m, Ar*H*), 7.17 (1H, dd, *J* 8.0, 1.0, Ar*H*), 6.46 (1H, dd, *J* 5.6, 3.0, CH_A=CH_B), 6.01 (1H, dd, *J* 5.6, 2.9, CH_A=CH_B), 4.09 (1H, dd, *J* 5.3, 3.1, C*H*Ar), 3.39–3.36 (1H, m, C*H*CH_2), 3.30–3.25 (1H, m, C*H*CH_2), 2.62–2.59 (1H, app dt, *J* 5.3, 2.1, C*H*CHO), 1.69–1.62 (1H, m, CH_AH_B) and 1.61–1.55 (1H, m, CH_AH_B).

***endo*-(2*R*)**: δ_H (300 MHz, $CDCl_3$) 9.40 (1H, d, *J* 3.7, C*H*O), 7.82 (1H, dd, *J* 8.1, 1.2, Ar*H*), 7.61–7.51 (2H, m, Ar*H*), 7.46–7.30 (1H, m, Ar*H*), 6.50 (1H, dd, *J* 5.7, 3.3, CH_A=CH_B), 6.21 (1H, dd, *J* 5.7, 2.8, CH_A=CH_B), 3.43 (1H, dd, *J* 5.2, 1.2, C*H*Ar), 3.34–3.29 (1H, m, C*H*CH_2), 3.14–3.10 (1H, m, C*H*CH_2), 2.95 (1H, app dt, *J* 5.2, 3.7, C*H*CHO), 1.84 (1H, app dt, 9.0, 1.6, CH_AH_B) and 1.69–1.62 (1H, m, CH_AH_B).

Enantiomeric excess was determined by acetalisation with (+)-(*R,R*)-hydrobenzoin and ^{1}H NMR analysis:[67] (300 MHz, C_6D_6) *exo* isomers **δ** 5.59 (d, *J* 4.5, C*H*O_2, 2*R*) and 5.51 (d,

J 5.1, C*H*O$_2$, 2*S*), *endo* isomers ***δ*** 5.21 (d, *J* 7.6, C*H*O$_2$, 2*R*) and 5.13 (d, *J* 7.6, C*H*O$_2$, 2S).

exo-(1*R*,2*R*,3*R*,4*S*)-3-(Naphthalen-2-yl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and _endo_-(1*S*,2*R*,3*R*,4*R*)-3-(naphthalen-2-yl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 5.4, entry 6)



***exo*-(2*R*)** ***endo*-(2*R*)**

Following the method of Baldwin *et al.*,[142] 2-naphthaldehyde (1.11 g, 7.11 mmol) in toluene (7 mL) was heated to 80 ºC and (triphenylphosphoranylidene) acetaldehyde (2.16 g, 7.11 mmol) was added portionwise and the resulting mixture stirred at 80 ºC for 7 h. The solvent was the removed *in vacuo* ((*Z*):(*E*) 14:86) and the crude material purified by column chromatography, eluting with 60 % dichloromethane in petrol to give (*E*)-3-(naphthalen-2-yl)acrylaldehyde as a yellow solid, with spectroscopic data in accordance with the literature (210 mg, 16 %).[143]

δ_H_ (300 MHz, $CDCl_3$) 9.77 (1H, d, *J* 7.7, C*H*O), 8.00 (1H, s, CAr(1)*H*), 7.91–7.85 (3H, m, Ar*H*), 7.69 (1H, dd, *J* 8.4, 1.7, ArH), 7.65 (1H, d, *J* 15.8, C*H*CHCHO), 7.60–7.51 (2H, m, Ar*H*), and 6.84 (1H, dd, *J* 15.8, 7.7, C*H*CHO).

(*E*)-3-(Naphthalen-2-yl)acrylaldehyde (173 mg, 0.950 mmol), triflic acid (0.190 M solution in methanol, 0.5 mL, 95.0 μmol), catalyst **(5*R*)-163** (10 mol%, 37.0 mg, 95.0 μmol) and cyclopentadiene (188 mg, 2.80 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 50 % dichloromethane in petrol to yield the title compounds as a 38:62 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (187 mg, 86 %).

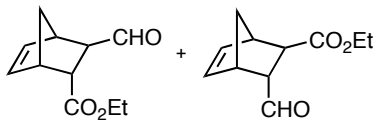
exo*-(2*R*): δ_H_*** (300 MHz, $CDCl_3$) 9.98 (1H, d, *J* 2.0, C*H*O), 7.82–7.72 (3H, m, Ar*H*), 7.55 (1H, s, CAr(1)*H*), 7.49–7.37 (2H, m, Ar*H*), 7.32 (1H, dd, *J* 8.6, 1.9, Ar*H*), 6.38 (1H, dd, *J* 5.6, 3.1, CH_A=CH_B), 6.09 (1H, dd, *J* 5.6, 2.9, CH_A=CH_B), 3.90 (1H, dd, *J* 5.1, 3.5, C*H*Ar), 3.35–3.30 (1H, m, C*H*CH_2), 3.30–3.23 (1H, m, C*H*CH_2), 2.74 (1H, app dt, *J* 5.1, 1.8, C*H*CHO), 1.71–1.65 (1H, m, CH_AH$_B$) and 1.64–1.57 (1H, m, CH$_A$$H_B$).

endo*-(2*R*): δ_H_*** (300 MHz, $CDCl_3$) 9.66 (1H, d, *J* 2.2, C*H*O), 7.82–7.72 (3H, m, Ar*H*), 7.69 (1H, s, CAr(1)*H*), 7.49–7.37 (3H, m, Ar*H*), 6.47 (1H, dd, *J* 5.7, 3.2, CH_A=CH$_B$), 6.21 (1H, dd, *J* 5.7, 2.7, CH$_A$=CH_B), 3.42–3.37 (1H, m, C*H*CH_2), 3.30–3.23 (2H, m, C*H*CH_2 & C*H*Ar), 3.09 (1H,

app dt, *J* 8.7, 1.8, C*H*CHO), 1.90 (1H, app dt, *J* 8.7, 1.6, CH_AH$_B$) and 1.71–1.65 (1H, m, CH$_A$$H_B$).

Enantiomeric excess was determined by acetalisation with (+)-(*R,R*)-hydrobenzoin and ^{1}H NMR analysis: (400 MHz, C_6D_6) *exo* isomers **δ** 5.81 (d, *J* 4.7, C*H*O$_2$, 2*R*) and 5.78 (d, *J* 5.9, C*H*O$_2$, 2*S*), *endo* isomers **δ** 5.44 (d, *J* 8.1, C*H*O$_2$, 2*R*) and 5.39 (d, *J* 8.2, C*H*O$_2$, 2*S*).

exo-(1*R*,2*R*,3*R*,4*S*)-Ethyl 3-formylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and _endo_-(1*S*,2*R*,3*R*,4*R*)-ethyl 3-formylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5.4, entry 9)

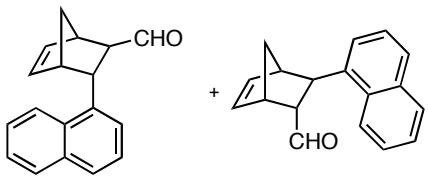


***exo*-(2*R*)** ***endo*-(2*R*)**

Ethyl (*E*)-4-oxo-2-butenoate (0.120 mL, 0.950 mmol), triflic acid (0.190 M solution in methanol, 0.5 mL, 95.0 μmol), catalyst **(5*R*)-163** (10 mol%, 37.0 mg, 95.0 μmol) and cyclopentadiene (188 mg, 2.80 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 15 % diethyl ether in petrol to yield the title compounds as a 44:56 mixture of diastereoisomers, with spectroscopic data identical to that of the racemate (129 mg, 84 %).

Enantiomeric excess was determined by derivatisation to the corresponding benzyl esters, following general procedure F and HPLC with ChiralPax AD-H column (2 % isopropanol:hexane, flow rate = 0.5 mL min^{-1}, 230 nm), *exo* t_R(2*S*) 19.0 min and t_R(2*R*) 21.9 min, *endo* t_R(2*S*) 23.3 min and t_R(2*R*) 25.1 min.[48]

exo-(1*R*,2*R*,3*R*,4*S*)-3-(Naphthalen-1-yl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and _endo_-(1*S*,2*R*,3*R*,4*R*)-3-(naphthalen-1-yl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 5.6, entry 2)



***exo*-(2*R*)** ***endo*-(2*R*)**

Following the method of Moitessier *et al.*,[144] to a suspension of (*E*)-3-(naphthalen-1-yl)acrylic acid (990 mg, 5.00 mmol) and DMF (0.0400 mL, 0.500 mmol) in dichloromethane (30 mL) was

added oxalyl chloride (0.65 mL, 7.500 mmol) dropwise, leading to significant gas evolution. The resulting mixture was stirred at room temperature for 1 h then concentrated *in vacuo* to a yellow solid which was subsequently dissolved in THF (30 mL) and cooled to –78 ºC. Lithium tri-*tert*-butoxyaluminium hydride (1.33 g, 5.25 mmol) was then added portionwise and the resulting mixture left to stir for 1 h. The mixture was then allowed to warm to 0 ºC and stirred for a further 2 h before being quenched by addition of water (30 mL). The resulting suspension was passed through a layer of Ceilte and the cake washed with dichloromethane (50 mL). The filtrate was diluted further with water (50 mL) and the resulting biphasic mixture extracted. The aqueous layer was washed with dichloromethane (50 mL) and the combined organic layers were washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel, eluting with 60 % dichloromethane in petrol to give (*E*)-3-(naphthalen-1-yl)acrylaldehyde as a yellow solid with spectroscopic data in accordance with the literature (463 mg, 51 %).[145]

mp 43–44 ˚C; $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 9.87 (1H, d, *J* 7.7, C*H*O), 8.35 (1H, d, *J* 15.7, C*H*CHCHO), 8.20 (1H, d, *J* 8.5, Ar*H*), 7.98–7.91 (2H, m, Ar*H*), 7.84 (1H, d, *J* 7.1, Ar*H*), 7.66–7.52 (3H, m, Ar*H*) and 6.86 (1H, dd, *J* 15.7, 7.7, C*H*CHO).

(*E*)-3-(Naphthalen-1-yl)acrylaldehyde (87.5 mg, 0.480 mmol), triflic acid (0.0190 M solution in methanol, 0.25 mL, 4.80 μmol), catalyst **170** (1 mol%, 2.00 mg, 4.80 μmol) and cyclopentadiene (94 mg, 2.80 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 40 % dichloromethane in petrol to yield the title compounds as a 21:79 mixture of diastereoisomers (99 mg, 83 %).

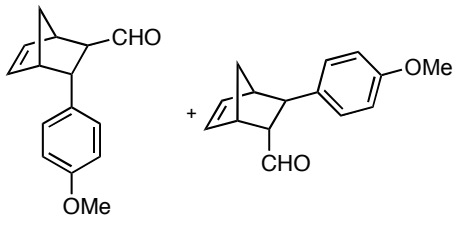
$\boldsymbol{[\alpha]^{20}_D}$ –47.3 (*c* 0.5, chloroform); $\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3051 (Ar-H), 2975 (C-H), 2872 (C-H), 2815 (C-H), 2717 (C-H), 1716 (C=O), 1597 (C=C) and 1578 (Ar C=C));

***exo*-(2*R*)**: $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 9.95 (1H, d, *J* 1.7, C*H*O), 8.32 (1H, d, *J* 8.4, Ar*H*), 7.89–7.84 (1H, m, Ar*H*), 7.76–7.70 (1H, m, Ar*H*), 7.61–7.42 (2H, m, Ar*H*), 7.35 (1H, t, *J* 7.7, Ar*H*), 7.09 (1H, d, *J* 8.4, Ar*H*), 6.45 (1H, dd, *J* 5.6, 3.2, CH_A=CH_B), 5.82 (1H, dd, *J* 5.6, 3.0, CH_A=CH_B), 4.58 (1H, dd, *J* 5.1, 3.5, C*H*Ar), 3.37–3.33 (1H, m, C*H*CH_2), 3.33–3.28 (1H, m, C*H*CH_2), 2.92 (1H, app dt, *J* 5.1, 1.7, C*H*CHO), 1.81 (1H, app dt, *J* 8.8, 1.5, CH_AH_B) and 1.62 (1H, ddd, *J* 8.8, 3.5, 1.8, CH_AH_B); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 202.6 (*C*HO), 139.2 (*C*H_A=CH_B), 137.6 (*C*Ar_{ipso}), 136.2 (*C*Ar_{ipso}), 134.1 (CH_A=*C*H_B), 132.5 (*C*Ar_{ipso}), 129.1 (*C*Ar), 127.2 (*C*Ar), 126.2 (*C*Ar), 125.6 (*C*Ar), 125.1 (*C*Ar), 123.4 (*C*Ar), 58.4 (*C*HCHO), 48.6 (*C*HCH_2), 47.9 (*C*H_2), 46.0 (*C*HCH_2) and 40.4 (*C*HAr).

endo*-(2*R*): δ_H*** (300 MHz, $CDCl_3$) 9.69 (1H, d, *J* 2.3, C*H*O), 8.05 (1H, dd, *J* 6.7, 2.5, Ar*H*), 7.89–7.84 (1H, m, Ar*H*), 7.76–7.70 (1H, m, Ar*H*), 7.61–7.42 (4H, m, Ar*H*), 6.58 (1H, dd, *J* 5.7, 3.2, CH_A=CH_B), 6.22 (1H, dd, *J* 5.7, 2.7, CH_A=CH_B), 3.82 (1H, dd, *J* 4.9, 1.1, C*H*Ar), 3.44–3.38 (1H, m, C*H*CH_2), 3.22 (1H, ddd, *J* 4.9, 3.5, 2.3, C*H*CHO), 3.20–3.17 (1H, m, C*H*CH_2), 1.92 (1H, app dt, *J* 8.7, 1.5, CH_AH_B) and 1.67 (1H, ddd, *J* 8.7, 3.2, 1.6, CH_AH_B); ***δ_C*** (75 MHz, $CDCl_3$) 203.5 (*C*HO), 139.1 (*C*H_A=CH_B), 136.9 (*C*Ar_{ipso}), 135.9 (*C*Ar_{ipso}), 134.2 (CH_A=*C*H_B), 132.5 (*C*Ar_{ipso}), 129.0 (*C*Ar), 127.3 (*C*Ar), 126.3 (*C*Ar), 125.8 (*C*Ar), 125.4 (*C*Ar), 123.8 (*C*Ar), 123.0 (*C*Ar), 59.1 (*C*HCHO), 49.7 (*C*HCH_2), 47.6 (*C*H_2), 45.7 (*C*HCH_2) and 41.4 (*C*HAr); ***m/z*** HRMS (ESI^+) $C_{18}H_{17}O$ ($[M+H]^+$) requires 249.1279, found 249.1287 (+3.0 ppm).

Enantiomeric excess was determined by acetalisation with (+)-(*R,R*)-hydrobenzoin and ^{1}H NMR analysis: (500 MHz, C_6D_6) *exo* isomers ***δ*** 5.79 (d, *J* 3.8, C*H*O_2, 2*R*) and 5.77 (d, *J* 5.1, C*H*O_2, 2*S*), *endo* isomers ***δ*** 5.51 (d, *J* 7.5, C*H*O_2, 2*R*) and 5.43 (d, *J* 7.7, C*H*O_2, 2*S*).

exo-(1*R*,2*R*,3*R*,4*S*)-3-(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and _endo_-(1*S*,2*R*,3*R*,4*R*)-3-(4-methoxyphenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5.6, entry 3)



***exo*-(2*R*)** ***endo*-(2*R*)**

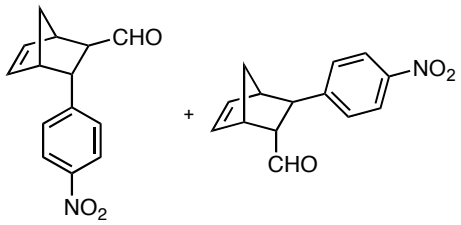
(*E*)-4-Methoxycinnamaldehyde (77.0 mg, 0.480 mmol), triflic acid (0.0190 M solution in methanol, 0.25 mL, 4.80 μmol), catalyst **170** (1 mol%, 2.00 mg, 4.80 μmol) and cyclopentadiene (94 mg, 2.80 mmol) were combined at 5 ºC according to general procedure D. The crude material was then purified by column chromatography, eluting with 10 % diethyl ether in petrol to yield the title compounds as a 36:64 mixture of diastereoisomers, with spectroscopic data in accordance with the literature (94 mg, 86 %).[70]

exo*-(2*R*)**: ***δ_H (400 MHz, $CDCl_3$) 9.91 (1H, d, *J* 2.0, C*H*O), 7.09–7.05 (2H, m, Ar*H*), 6.81–6.78 (2H, m, Ar*H*), 6.34 (1H, dd, *J* 5.6, 3.2, CH_A=CH_B), 6.07 (1H, dd, *J* 5.6, 2.9, CH_A=CH_B), 3.77 (3H, s, OCH_3), 3.66 (1H, dd, *J* 5.2, 3.5, C*H*Ar), 3.22–3.19 (1H, m, C*H*CH_2), 3.19–3.15 (1H, m, C*H*CH_2), 2.53 (1H, app dt, *J* 5.2, 2.0, C*H*CHO), 1.64–1.58 (1H, m, CH_AH_B) and 1.56–1.53 (1H, m, CH_AH_B).

***endo*-(2*R*)**: δ_H (400 MHz, $CDCl_3$) 958 (1H, d, *J* 2.3, C*H*O), 7.20–7.17 (2H, m, Ar*H*), 6.87–6.81 (2H, m, Ar*H*), 6.41 (1H, dd, *J* 5.6, 3.2, CH_A=CH_B), 6.16 (1H, dd, *J* 5.6, 2.8, CH_A=CH_B), 3.79 (3H, s, OCH_3), 3.33–3.29 (1H, m, C*H*Ar), 3.08–3.04 (1H, m, C*H*CH_2), 3.04–3.01 (1H, m, C*H*CH_2), 2.94 (1H, ddd, *J* 5.1, 3.2, 2.3, C*H*CHO), 1.79 (1H, app dt, *J* 8.7, 1.5, C$H_A$$H_B$) and 1.64–1.58 (1H, m, CH_AH_B).

Enantiomeric excess was determined by acetalisation with (+)-(*R,R*)-hydrobenzoin and ^{1}H NMR analysis:[70] (500 MHz, C_6D_6) *exo* isomers **δ** 5.76 (d, *J* 4.9, C*H*O_2, 2*R*) and 5.75 (d, *J* 7.0, C*H*O_2, 2*S*), *endo* isomers **δ** 5.39 (d, *J* 8.2, C*H*O_2, 2*R*) and 5.35 (d, *J* 8.2, C*H*O_2, 2*S*).

exo-(1*R*,2*R*,3*R*,4*S*)-3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and _endo_-(1*S*,2*R*,3*R*,4*R*)-3-(4-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5.6, entry 5)

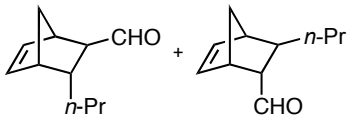


***exo*-(2*R*)** ***endo*-(2*R*)**

4-Nitrocinnamaldehyde (84.0 mg, predominantly (*E*)-, 0.480 mmol), triflic acid (96.0 mM solution in methanol, 0.25 mL, 24.0 μmol), catalyst **170** (5 mol%, 10.0 mg, 24.0 μmol) and cyclopentadiene (94.0 mg, 1.42 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 15 % ethyl acetate in petrol to yield the title compounds as a 36:64 mixture of diastereoisomers, with spectroscopic data identical to that of the racemate (106 mg, 91 %).

Enantiomeric excess was determined by acetalisation with (+)-(*R,R*)-hydrobenzoin and ^{1}H NMR analysis:[67] (500 MHz, C_6D_6) *exo* isomers **δ** 5.60 (d, *J* 5.2, C*H*O_2, 2*R*) and 5.58 (d, *J* 5.9, C*H*O_2, 2*S*), *endo* isomers **δ** 5.26 (d, *J* 8.1, C*H*O_2, 2*R*) and 5.19 (d, *J* 8.2, C*H*O_2, 2*S*).

***exo*-(1*R*,2*R*,3*R*,4*S*)-3-Propylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and *endo*-(1*S*,2*R*,3*R*,4*R*)-3-propylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 5.6, entry 6)**



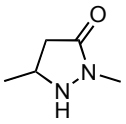
***exo*-(2*R*)** ***endo*-(2*R*)**

(*E*)-2-Hexen-1-al (0.110 mL, 0.950 mmol), triflic acid (0.0190 M solution in methanol, 0.5 mL, 9.50 μmol), catalyst **170** (1 mol%, 4.00 mg, 9.50 μmol) and cyclopentadiene (188 mg, 2.80 mmol) were combined according to general procedure D. The crude material was then purified by column chromatography, eluting with 2.5 % diethyl ether in petrol to yield the title compounds as a 31:69 mixture of diastereoisomers, with spectroscopic data identical to that of the racemate (140 mg, 90 %).

Enantiomeric excess was determined by acetalisation with (+)-(*R,R*)-hydrobenzoin and ^{1}H NMR analysis:[70] (300 MHz, C_6D_6) *exo* isomers **δ** 5.62 (d, *J* 6.1, C*H*O$_2$, 2*R*) and 5.60 (d, *J* 6.2, C*H*O$_2$, 2*S*), *endo* isomers **δ** 5.24 (d, *J* 8.3, C*H*O$_2$, 2*R*) and 5.18 (d, *J* 8.3, C*H*O$_2$, 2*S*).

7.3.2 Other experimental procedures

(*RS*)-2,5-dimethylpyrazolidin-3-one 67



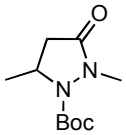
67

To a solution of (*RS*)-*tert*-butyl 2,5-dimethyl-3-oxopyrazolidine-1-carboxylate **73** (1.59 g, 7.42 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1.80 mL, 23.3 mmol) and the resulting solution stirred overnight at rt. TLC analysis of the crude reaction mixture showed incomplete reaction. Hence, further trifluoroacetic acid (0.580 mL, 7.51 mmol) was added and the mixture stirred overnight before concentration *in vacuo*. The resulting material was partitioned between dichloromethane (100 mL) and saturated sodium hydrogen carbonate solution (100 mL). The aqueous layer was washed with dichloromethane (100 mL) and the combined organic layers washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (145 mg). The aqueous layer was treated with triethylamine then extracted with further dichloromethane (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give further material (177 mg). The

aqueous layer was then concentrated *in vacuo* and partitioned between 1M sodium hydroxide solution (50 mL) and dichloromethane (80 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give further material (151 mg) (473 mg in total, 55 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3196 (N-H), 2969 (C-H), 2927 (C-H), 1667 (C=O), 1605 and 1597 (N-H bend); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 4.12 (1H, br s, N(1)*H*), 3.66 (1H, app dquin, *J* 8.3, 6.7, C(5)*H*), 3.01 (3H, s, N(2)CH_3), 2.59 (1H, dd, ABX system, J_{AB} 16.1, J_{AX} 7.2, C(4)H_AH$_B$), 2.20 (1H, dd, ABX system, J_{BA} 16.1, J_{BX} 8.3, C(4)H$_A$$H_B$) and 1.24 (3H, d, *J* 6.4, C(5)HCH_3); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 172.6 (*C*(3)O), 51.4 (*C*(5)H), 40.4 (*C*(4)H_2), 31.4 (N(2)*C*H_3) and 19.1 (C(5)H*C*H_3); ***m/z*** (CI) 115.2 (100, $[M+H]^+$); HRMS (ESI^+) $C_5H_{11}N_2O$ ($[M+H]^+$) requires 115.0866, found 115.0865 (–0.4 ppm).

(*RS*)-*tert*-Butyl 2,5-dimethyl-3-oxopyrazolidine-1-carboxylate 73

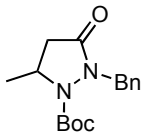


73

A solution of crude (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (2.92 g, 13.6 mmol) in DMF (30 mL) was treated with iodomethane (2.80 mL, 45.0 mmol) and potassium carbonate (2.49 g, 18.0 mmol) and the suspension stirred at rt overnight. The reaction mixture was partitioned between diethyl ether (60 mL) and water (60 mL) and the resultant aqueous layer washed with further diethyl ether (60 mL). The combined organic layers were washed with brine (120 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The material was then purified by column chromatography, eluting with 25 % ethyl acetate in petrol to give the title compound as a colourless oil with spectroscopic data in accordance with the literature (1.60 g, 53 %).[76]

$\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 4.53 (1H, app quin, *J* 7.0, C(5)*H*), 3.20 (3H, s, N(2)CH_3), 2.91 (1H, dd, *J* 16.3, 8.3, C(4)H_AH$_B$), 2.00 (1H, d, *J* 16.3, C(4)H$_A$$H_B$), 1.48 (9H, s, C(C$H_3$)$_3$) and 1.22 (3H, d, *J* 6.8, C(5)HCH_3).

(*RS*)-*tert*-Butyl 2-benzyl-5-methyl-3-oxopyrazolidine-1-carboxylate 74



74

To a solution of hydrazine hydrate (9.02 mL, 0.180 mol) in absolute ethanol (200 mL) was added ethyl crotonate **66** (21.0 mL, 0.169 mol) by dropwise addition. The resulting solution was stirred for 1 h at rt and then at reflux for 4 h before concentration *in vacuo* to give crude (*RS*)-5-methylpyrazolidin-3-one **71** (18.1 g) as a viscous yellow oil with spectroscopic data in accordance with the literature.[75] Product was used without further purification.

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 3.78–3.66 (1H, app dquin, *J* 8.7, 6.7, C(5)*H*), 2.48 (1H, dd, ABX system, J_{AB} 16.1, J_{AX} 7.1, C(4)H_AH$_B$), 2.12 (1H, dd, ABX system, J_{BA} 16.1, J_{BX} 8.7, C(4)H$_A$$H_B$) and 1.22 (3H, d, *J* 6.3, C(5)HCH_3).

To a solution of crude (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **71** (18.1 g, 0.180 mol) in water (100 mL) was added sodium carbonate (19.1 g 0.180 mol) and dioxane (50 mL). A solution of di-*tert*-butyl dicarbonate (39.3 g, 0.240 mol) in dioxane (50 mL) was then added and the mixture stirred at rt for 1 h. The resulting suspension was filtered and the precipitate washed with chloroform. The combined organic extracts were then concentrated *in vacuo* to approximately 30 mL volume and partitioned between water (100 mL) and dichloromethane (100 mL). The organic extracts were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (33.9 g) as a yellow solid with spectroscopic data in accordance with the literature.[76] Product was used without further purification.

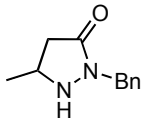
$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.50 (1H, br s, N(2)*H*), 4.38 (1H, dqd, *J* 9.6, 6.5, 3.3, C(5)*H*), 2.92 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 9.6, C(4)H_AH$_B$), 2.14 (1H, dd, ABX system, J_{BA} 17.0, J_{BX} 3.3, C(4)H$_A$$H_B$), 1.43 (9H, s, C($CH_3$)$_3$ and 1.29 (3H, d, *J* 6.5, C(5)HCH_3).

A solution of crude (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (33.9 g, 170 mmol) in DMF (125 mL) was treated with benzyl bromide (20.2 mL, 170 mmol) and potassium carbonate (23.9 g, 173 mmol) and the suspension stirred at rt for 2.5 h. The reaction mixture was partitioned between diethyl ether (150 mL) and water (250 mL) and the resultant aqueous layer washed with further diethyl ether (2 x 150 mL). The combined organic layers were washed with water (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography, eluting with 25 % ethyl

acetate in petrol to give the title compound as a colourless solid (19.9 g, 41 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3028 (Ar-H), 2976 (C-H), 2931 (C-H), 2871 (N-C-H), 1706 (C=O), 1690 (C=O), 1557 (Ar C=C) and 1534 (Ar C=C); ***mp*** 90–94 ºC; $\boldsymbol{\delta_N}$ ($CDCl_3$) 156 (*N*(2)CH_2Ph), 136 (*N*(1)Boc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.35–7.29 (5H, m, Ar*H*), 5.29 (1H, d, AB system, J_{AB} 14.2, C$H_A$$H_B$Ph), 4.42 (1H, app quin, *J* 7.2, C(5)*H*), 4.39 (1H, d, AB system, J_{BA} 14.2, C$H_A$$H_B$Ph), 2.95 (1H, dd, *J* 16.3, 8.2, C(4)$H_A$$H_B$), 1.96 (1H, d, *J* 16.3, C(4)$H_A$$H_B$), 1.56 (9H, s, C(C$H_3$)$_3$) and 0.65 (3H, d, *J* 6.7, C(5)HCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.5 (*C*(3)O), 156.1 (*C*(O)O), 135.6 (*C*Ar$_{ipso}$), 129.7 (*C*Ar), 128.4 (*C*Ar), 128.1 (*C*Ar), 82.6 (*C*$(CH_3)_3$), 53.7 (*C*(5)H), 48.6 (*C*H_2Ph), 38.1 (*C*(4)H_2), 28.3 (C(*C*H_3)$_3$) and 19.7 (C(5)H*C*H_3); ***m/z*** (CI) 291.3 (100, $[M+H]^+$); HRMS (ESI^+) $C_{16}H_{23}N_2O_3$ ($[M+H]^+$) requires 291.1703, found 291.1705 (+0.7 ppm).

(*RS*)-2-Benzyl-5-methylpyrazolidin-3-one 76



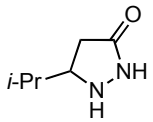
76

(*RS*)-*tert*-Butyl 2-benzyl-5-methyl-3-oxopyrazolidine-1-carboxylate **74** (2.84 g, 9.78 mmol) was stirred at rt overnight in a 1:1 mixture of trifluoroacetic acid/dichloromethane (8 mL) before being concentrated *in vacuo.* The resulting material was redissolved in dichloromethane (6 mL), cooled to 0 ºC before treatment with triethylamine (2.40 mL, 17.2 mmol). The resulting solution was stirred at rt for a further 15 min before being partitioned between water (40 mL) and dichloromethane (40 mL). The resultant aqueous layer was washed with dichloromethane (40 mL) and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was then purified by column chromatography, eluting with 5 % methanol in ethyl acetate to give the title compound as a clear yellow oil (1.42 g, 76 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3202 (N-H), 3063 (Ar-H), 3031 (Ar-H), 2970 (C-H), 2925 (C-H), 2868 (N-C-H), 1678 (C=O), 1605 (Ar C=C) and 1583 (N-H bend); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.40–7.30 (5H, m, Ar*H*), 4.70 (1H, d, AB system, J_{AB} 14.6, C$H_A$$H_B$Ph), 4.55 (1H, d, AB system, J_{BA} 14.6, C$H_A$$H_B$Ph), 4.10 (1H, br s, N(1)*H*), 3.69 (1H, app dquin, *J* 8.3, 6.7, C(5)*H*), 2.71 (1H, dd, ABX system, J_{AB} 16.2, J_{AX} 7.1, C(4)$H_A$$H_B$), 2.29 (1H, dd, ABX system, J_{BA} 16.2, J_{BX} 8.3, C(4)$H_A$$H_B$) and 1.25 (3H, d, *J* 6.4, C(5)HCH_3); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 175.7 (*C*(3)O), 139.2 (*C*Ar$_{ipso}$), 132.1 (*C*Ar), 131.6 (*C*Ar), 131.1 (*C*Ar), 54.8 (*C*(5)H), 51.4 (*C*H_2Ph),

43.8 (*C*(4)H_2) and 22.1 (C(5)H*C*H_3); ***m/z*** (CI) 191.2 (100, $[M+H]^+$); HRMS (ESI^+) $C_{11}H_{15}N_2O$ ($[M+H]^+$) requires 191.1179, found 191.1177 (–0.8 ppm).

(*RS*)-5-*iso*-propylpyrazolidin-3-one 79

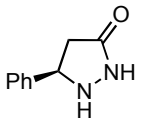


79

To a solution of *iso*-butyrlaldehyde (2.17 mL, 24.0 mmol) in dichloromethane (100 mL), cooled to 0 ºC, was added ethyl (triphenylphosphoranylidene)acetate **77** (10.0 g, 29.0 mmol) and the resulting clear yellow solution stirred at rt overnight before being concentrated *in vacuo*. The crude material was then passed through a plug of silica gel, eluting with 3 % ethyl acetate in petrol. The resulting crude residue was then dissolved in absolute ethanol (3 mL), hydrazine hydrate (70.0 μL, 1.48 mmol) was added and the solution stirred for 1 h at rt and then at reflux for 4 h before concentration *in vacuo.* The crude material was purified by column chromatography, eluting with 5 % methanol in dichloromethane, then flushed with 20 % methanol in dichloromethane to give the product as a clear yellow oil (2.68 g, 87 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3401 (N-H), 3214 (N-H), 2961 (C-H), 2931 (C-H), 2874 (N-C-H) and 1683 (C=O); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 3.33 (1H, app dt, *J* 9.4, 7.7, C(5)*H*), 2.43 (1H, dd, ABX system, J_{AB} 16.4, J_{AX} 7.4, C(4)H_AH_B), 2.23 (1H, dd, ABX system, J_{BA} 16.4, J_{BX} 9.4, C(4)H_AH_B), 1.67 (1H, dsept, *J* 7.9, 6.5 C(5)HC*H*). 0.94 (3H, d, *J* 6.5 CH(CH_3)$_A$(CH_3)$_B$) and 0.89 (3H, d, *J* 6.5, CH(CH_3)$_A$(CH_3)$_B$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 177.6 (*C*(3)O), 65.6 (*C*(5)H), 36.6 (*C*(4)H_2), 32.5 (C(5)H*C*H), 19.7 (CH(*C*H_3)$_A$(CH_3)$_B$) and 19.6 (C(4)(CH_3)$_A$(*C*H_3)$_B$); ***m/z*** (CI) 129.1 (100, $[M+H]^+$); HRMS (CI) $C_6H_{13}N_2O$ ($[M+H]^+$) requires 129.1028, found 129.1032 (+3.2 ppm).

(*R*)-5-phenylpyrazolidin-3-one (*R*)-83



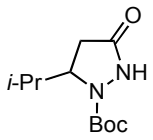
(*R*)-83

(*R*)-2-((*R*)-2-Methoxy-2-phenylacetyl)-5-phenylpyrazolidin-3-one **(5*R*)-134** (4.62 g, 14.9 mmol) was suspended in 6 M aqueous hydrochloric acid solution (40 mL) and heated to reflux for 30 min. The reaction mixture was basified with 2 M sodium hydroxide solution

(150 mL) and extracted with dichloromethane (3 x 150 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a small quantity of the title compound (191 mg). Hence, the aqueous phase was neutralised to pH 7 with 37 % hydrochloric acid solution and again extracted with dichloromethane (3 x 150 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a further 1.20 g of the title compound as a colourless solid, with spectroscopic data identical to **83** (1.39 g, 57 %).

$[\alpha]^{20}_D$ −13.0 (*c* 1.0, methanol); ***mp*** 94–96 ºC.

(*RS*)-*tert*-Butyl 5-*iso*-propyl-3-oxopyrazolidine-1-carboxylate 86



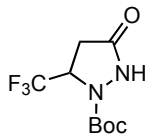
86

To a solution of (*RS*)-5-*iso*-propylpyrazolidin-3-one **79** (578 mg, 4.51 mmol) in water (6 mL) was added sodium carbonate (503 mg, 4.75 mmol) and dioxane (3 mL). A solution of di-*tert*-butyl dicarbonate (1.02 g, 4.67 mmol) in dioxane (3 mL) was then added and the mixture stirred at rt overnight. TLC analysis showed incomplete reaction. Hence, more sodium carbonate (240 mg, 2.26 mmol) and di-*tert*-butyl dicarbonate (490 mg, 2.24 mmol) in dioxane (1 mL) were added and the mixture stirred for a further 3 h. The resulting suspension was then filtered and the precipitate washed with chloroform. The combined organic extracts were then concentrated *in vacuo* to approximately 5 mL volume and partitioned between water (40 mL) and dichloromethane (40 mL). The aqueous layer was washed with further dichloromethane (2 x 40 mL) and then the combined organic extracts washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography, eluting with 2 % methanol in dichloromethane to give the product as an off-white solid (530 mg, 51 %).

ν_{max} (film)/ cm^{-1} 3171 (N-H), 3072 (N-H), 2970 (C-H), 2933 (C-H), 2877 (N-C-H), 1698 (C=O) and 1676 (C=O); ***mp*** 80–81 ºC; δ_H (300 MHz, $CDCl_3$) 4.13 (1H, ddd, *J* 9.8, 6.4, 2.5, C(5)*H*), 2.80 (1H, dd, ABX system, J_{AB} 17.3, J_{AX} 9.8, C(4)H_AH_B), 2.23 (1H, dd, ABX system, J_{BA} 17.3, J_{BX} 2.5, C(4)H_AH_B), 1.84 (1H, app oct, *J* 6.6, C(5)HC*H*). 1.43 (9H, s, C(CH_3)$_3$) and 0.88 (6H, d, *J* 6.8, CH(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 170.7 (*C*(3)O), 154.7 (*C*(O)O), 82.6 (*C*(CH_3)$_3$), 62.1 (*C*(5)H), 33.6 (*C*(4)H_2), 32.3 (C(5)H*C*H), 28.3 (C(*C*H_3)$_3$),

17.9 ($CH(CH_3)_A(CH_3)_B$) and 17.7 ($C(4)(CH_3)_A(CH_3)_B$); ***m/z*** (CI) 190.3 (100, $[M-C(CH_3)_3+NH_4]^+$), 229.3 (35, $[M+H]^+$); HRMS (ESI^+) $C_{11}H_{21}N_2O_3$ ($[M+H]^+$) requires 229.1547, found 229.1547.

(*RS*)-*tert*-Butyl 3-oxo-5-(trifluoromethyl)pyrazolidine-1-carboxylate 87



87

To a solution of hydrazine hydrate (1.60 mL, 32.7 mmol) in absolute ethanol (50 mL) was added ethyl 4,4,4-trifluorocrotonate **82** (4.40 mL, 29.3 mmol) and the resulting solution stirred at reflux for 3 h before concentration *in vacuo* to give crude (*RS*)-5-(trifluoromethyl)-pyrazolidin-3-one **84** (3.35 g) as a yellow solid. Product was used without further purification. An analytical sample was taken and purified by recrystallisation in hot toluene to give the title compound as colourless plates.

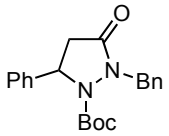
ν_{max} (KBr disc)/ cm^{-1} 3248 (N-H), 3190 (N-H), 1694 (C=O) and 1648 (N-H bend); ***mp*** 130–132 ºC; ***δ_F*** (375 MHz, CD_3OD) −81.0 (3F, d, *J* 8.2, CF_3); ***δ_H*** (300 MHz, CD_3OD) 4.18 (1H, dqd, *J* 10.3, 8.2, 2.6, C(5)*H*), 3.02 (1H, dd, ABX system, J_{AB} 17.4, J_{AX} 10.3, $C(4)H_AH_B$) and 2.42 (1H, dd, ABX system, J_{BA} 17.4, J_{BX} 2.6, $C(4)H_AH_B$); ***δ_C*** (75 MHz, CD_3OD) 174.2 (*C*(3)O), 125.2 (q, *J* 279, CF_3), 56.2 (q, *J* 31.4, *C*(5)H) and 31.0 (q, *J* 1.5, $C(4)H_2$); ***m/z*** HRMS (ESI^+) $C_4H_9F_3N_3O$ ($[M+NH_4]^+$) requires 172.0692, found 172.0688 (−2.6 ppm).

To a solution of crude (*RS*)-5-(trifluoromethyl)pyrazolidin-3-one **84** (2.62 g, 17.0 mmol) in water (20 mL) was added sodium carbonate (1.80 g, 17.0 mmol) and dioxane (10 mL). A solution of di-*tert*-butyl dicarbonate (3.70 g, 17.0 mmol) in dioxane (10 mL) was then added and the mixture stirred at rt overnight. The resulting suspension was filtered and the precipitate washed with ethyl acetate. The combined organic extracts were then concentrated *in vacuo* to a small volume at which point the title compound began to precipitate. This solid was collected by filtration and washed with water. The combined filtrate was cooled to 0 ºC overnight to yield a second crop of the title compound which was collected by filtration and washed with further cold water. The combined solids were dried in a desiccator to give the title compound as a colourless solid (2.64 g, 35 %).

ν_{max} (film)/ cm^{-1} 3343 (N-H), 3010 (N-H), 2986 (C-H), 1717 (C=O) and 1697 (C=O);

mp 141–144 ºC; $\boldsymbol{\delta}_F$ (375 MHz, $CDCl_3$) −79.3 (3F, d, *J* 6.7, C*F*$_3$); $\boldsymbol{\delta}_H$ (300 MHz, $CDCl_3$) 4.89 (1H, dqd, *J* 10.6, 6.7, 2.3, C(5)*H*), 3.08 (1H, dd, ABX system, J_{AB} 17.8, J_{AX} 10.6, C(4)H_AH_B), 2.64 (1H, dd, ABX system, J_{BA} 17.8, J_{BX} 2.3, C(4)H_AH_B) and 1.52 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta}_C$ (100 MHz, $CDCl_3$) 168.7 (*C*(3)O), 154.0 (*C*(O)O), 124.0 (q, *J* 281, *C*F$_3$), 84.7 *C*(CH$_3$)$_3$), 56.7 (q, *J* 34.0, *C*(5)H), 30.8 (*C*(4)H$_2$) and 28.1 (C(*C*H$_3$)$_3$); ***m/z*** HRMS (ESI$^+$) $C_9H_{14}F_3N_2O_3$ ([M+H]$^+$) requires 255.0951, found 255.0954 (+1.2 ppm).

(*RS*) *tert*-Butyl 2-benzyl-3-oxo-5-phenylpyrazolidine-1-carboxylate 88



88

To a solution of hydrazine hydrate (1.45 mL, 29.8 mmol) in absolute ethanol (25 mL) was added ethyl cinnamate **81** (5.00 mL, 29.8 mmol) and the resulting solution stirred at reflux overnight. The suspension was then concentrated *in vacuo* and redissolved in toluene (25 mL) and stirred at reflux for 3 h. The resulting solution was concentrated *in vacuo* to give crude (*RS*)-5-phenylpyrazolidin-3-one **83** (3.62 g) as a brown solid. Product was used without further purification. An analytical sample was taken and purified by recrystallisation in hot toluene to give the title compound as an off-white solid.

$\boldsymbol{\nu}_{max}$ (KBr disc)/ cm^{-1} 3234 (N-H), 3191 (N-H), 3051 (Ar-H), 3019 (C-H), 1715 (C=O), 1664 (N-H bend) and 1599 (Ar C=C); ***mp*** 95–97 ºC; $\boldsymbol{\delta}_H$ (400 MHz, $CDCl_3$) 7.44–7.32 (5H, m, Ar*H*), 4.84 (1H, app t, *J* 8.5, C(5)*H*), 2.85 (1H, dd, ABX system, J_{AB} 16.2, J_{AX} 7.6, C(4)H_AH_B) and 2.76 (1H, dd, ABX system, J_{BA} 16.2, J_{BX} 9.4, C(4)H_AH_B); $\boldsymbol{\delta}_C$ (100 MHz, $CDCl_3$) 176.7 (*C*(3)O), 138.4 (*C*Ar$_{ipso}$), 129.1 (*C*Ar), 128.6 (*C*Ar), 126.7 (*C*Ar), 62.0 (*C*(5)H) and 38.3 (*C*(4)H$_2$); ***m/z*** (ES) 185.0 (100, [M+Na]$^+$), 163.2 (100, [M+H]$^+$); HRMS (ESI$^+$) $C_9H_{11}N_2O$ ([M+H]$^+$) requires 163.0866, found 163.0867 (+0.6 ppm).

To a solution of crude (*RS*)-5-phenylpyrazolidin-3-one **83** (3.62 g, 22.3 mmol) in water (30 mL) was added sodium carbonate (2.37 g 22.3 mmol) and dioxane (10 mL). A solution of di-*tert*-butyl dicarbonate (4.90 g, 22.4 mmol) in dioxane (10 mL) was then added and the mixture stirred at rt for 3 h. The resulting suspension was filtered and the precipitate washed with chloroform. The combined organic extracts were then concentrated *in vacuo* to approximately 30 mL volume and partitioned between water (100 mL) and dichloromethane (75 mL). The aqueous layer was extracted with further dichloromethane (2 x 75 mL) and then the combined

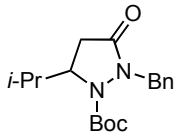
organic extracts washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude (*RS*)-*tert*-butyl 5-phenyl-3-oxopyrazolidine-1-carboxylate **85** (4.95 g) as a yellow oil. Product was used without further purification. An analytical sample was taken and purified by column chromatography, eluting with 50 % dichloromethane in petrol, then 5 % methanol in dichloromethane to give the title compound as a colourless solid.

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3334 (N-H), 3016 (Ar-H), 2965 (C-H), 1707 (C=O) and 1681 (C=O); ***mp*** 134–137 ºC; $\boldsymbol{\delta_N}$ ($CDCl_3$) 147 (*N*(1)Boc, 127 (*N*(2)H); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.36–7.27 (5H, m, Ar*H*), 5.33 (1H, dd, *J* 10.4. 3.9, C(5)*H*), 3.30 (1H, dd, ABX system, J_{AB} 17.3, J_{AX} 10.4, C(4)H_AH_B), 2.63 (1H, dd, ABX system, J_{BA} 17.3, J_{BX} 3.9, C(4)H_AH_B) and 1.36 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 169.6 (*C*(3)O), 153.7 (*C*(O)O), 141.2 (*C*Ar$_{ipso}$), 129.3 (*C*Ar), 128.5 (*C*Ar), 126.1 (*C*Ar), 83.2 (*C*$(CH_3)_3$), 59.9 (*C*(5)H), 40.0 (*C*(4)H_2) and 28.5 (C(*C*H_3)$_3$); ***m/z*** (CI) 224.2 (100, [M-C$(CH_3)_3$+NH_4]$^+$), 263.3 (20, [M+H]$^+$); HRMS (ESI$^+$) $C_{14}H_{19}N_2O_3$ ([M+H]$^+$) requires 263.1390, found 263.1392 (+0.7 ppm).

A solution of crude (*RS*)-*tert*-butyl 5-phenyl-3-oxopyrazolidine-1-carboxylate **85** (4.95 g, 18.9 mmol) in DMF (25 mL) was treated with benzyl bromide (2.25 mL, 18.9 mmol) and potassium carbonate (2.61 g, 18.9 mmol) and the suspension stirred at rt for 90 min. The reaction mixture was partitioned between diethyl ether (50 mL) and water (50 mL) and the resultant aqueous layer washed with further diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The material was then purified by column chromatography, eluting with 20 % ethyl acetate in petrol. Chromatography was then repeated, this time eluting with 15–20 % ethyl acetate in petrol to give the title compound as a yellow oil (2.63g, 25 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3064 (Ar-H), 3032 (Ar-H), 2978 (C-H), 2933 (C-H), 2873 (N-C-H), 1750–1658 (2 x C=O), 1604 (Ar C=C) and 1587 (Ar C=C); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.28–7.24 (1H, m, Ar*H*), 7.21–7.12 (5H, m, Ar*H*), 7.04 (2H, t, *J* 7.5, Ar*H*), 6.70 (2H, d, *J* 7.5, Ar*H*), 5.45 (1H, app d, *J* 9.3, C(5)*H*), 5.31 (1H, d, AB system, J_{AB} 14.2, C$H_A$$H_B$Ph), 4.59 (1H, d, AB system, J_{BA} 14.2, C$H_A$$H_B$Ph), 3.30 (1H, dd, *J* 16.8, 9.5, C(4)$H_A$$H_B$), 2.66 (1H, d, *J* 16.8, C(4)$H_A$$H_B$) and 1.56 (9H, s, C(C$H_3$)$_3$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 170.5 (*C*(3)O), 156.7 (*C*(O)O), 139.5 (*C*Ar$_{ipso}$), 135.7 (*C*Ar$_{ipso}$), 130.1 (*C*Ar), 128.8 (*C*Ar), 128.4 (*C*Ar), 127.8 (*C*Ar), 126.1 (*C*Ar), 83.4 (*C*$(CH_3)_3$), 60.2 (*C*(5)H), 49.2 (*C*H_2Ph), 37.8 (*C*(4)H_2) and 28.7 (C(*C*H_3)$_3$); ***m/z*** (CI) 353.3 (100, [M+H]$^+$); HRMS (ESI$^+$) $C_{21}H_{25}N_2O_3$ ([M+H]$^+$) requires 353.1860, found 353.1863 (+0.8 ppm).

(*RS*)-*tert*-Butyl 2-benzyl-5-*iso*-propyl-3-oxopyrazolidine-1-carboxylate 89

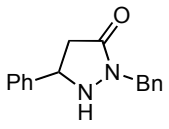


89

A solution of crude (*RS*)-*tert*-butyl 5-*iso*-propyl-3-oxopyrazolidine-1-carboxylate **86** (498 mg, 2.18 mmol) in DMF (2 mL) was treated with benzyl bromide (0.260 mL, 2.18 mmol) and potassium carbonate (301 mg, 2.18 mmol) and the suspension stirred at rt for 60 min. The reaction mixture was partitioned between diethyl ether (20 mL) and water (20 mL) and the resultant aqueous layer washed with further diethyl ether (2 x 20 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The material was then purified by column chromatography, eluting with 20 % ethyl acetate in petrol. Chromatography was then repeated, this time eluting with 15–25 % ethyl acetate in petrol to give the title compound as a crystalline yellow solid (281 mg, 41 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3067 (Ar-H), 3035 (Ar-H), 2971 (C-H), 2928 (C-H), 2862 (N-C-H), 1744–1661 (2 x C=O), 1602 (Ar C=C) and 1586 (Ar C=C); ***mp*** 53–56 ºC; $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.23 (5H, app bs, Ar*H*), 5.21 (1H, d, AB system, J_{AB} 14.0, CH_AH_BPh), 4.39 (1H, d, AB system, J_{BA} 14.0, CH_AH_BPh)**,** 3.76 (1H, app t, *J* 9.3, C(5)*H*), 2.78 (1H, dd, J_{AB} 16.6, 8.7, C(4)H_AH_B), 2.14 (1H, d, *J* 16.6, C(4)H_AH_B), 1.45 (9H, s, $C(CH_3)_3$), 0.88 (1H, dsept, *J* 10.2, 6.6, C(5)HC*H*), 0.61 (3H, d, *J* 6.6, $CH(CH_3)_A(CH_3)_B$) and 0.24 (3H, d, *J* 6.6, $CH(CH_3)_A(CH_3)_B$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 170.9 (*C*(3)O), 156.6 (*C*(O)O), 135.7 (Ar_{ipso}), 129.7 (*C*Ar), 128.4 (*C*Ar), 128.2 (*C*Ar), 82.4 ($C(CH_3)_3$), 64.1 (*C*(5)H), 48.6 (CH_2Ph), 34.9 (*C*(4)H_2), 30.8 (C(5)HCH), 28.3 ($C(CH_3)_3$), 18.5 ($CH(CH_3)_A(CH_3)_B$) and 18.3 ($C(4)(CH_3)_A(CH_3)_B$); ***m/z*** (CI) 219.3 (100, $[M\text{-}CO_2C(CH_3)_3+NH_4]^+$), 319.2 (60, $[M+H]^+$); HRMS (ESI^+) $C_{18}H_{27}N_2O_3$ ($[M+H]^+$) requires 319.2016, found 319.2019 (–0.8 ppm).

(*RS*)-2-Benzyl-5-phenylpyrazolidin-3-one 91



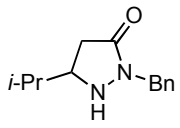
91

To a solution of (*RS*)-*tert*-butyl 2-benzyl-5-phenyl-3-oxopyrazolidine-1-carboxylate **88** (2.28 g, 6.48 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (5.00 mL, 64.8 mmol) and the resulting mixture stirred at rt overnight. The excess acid was then quenched with

saturated sodium hydrogen carbonate solution (150 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as an off-white solid on standing (1.59 g, 97 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3214 (N-H), 3062 (Ar-H), 3031 (Ar-H), 2920 (C-H), 1683 (C=O), 1604 (Ar C=C) and 1560 (N-H bend); ***mp*** 60–62 ºC; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.26–7.18 (5H, m, Ar*H*), 4.62 (1H, d, AB system, J_{AB} 14.6, CH_AH$_B$Ph), 4.58 (1H, app t, *J* 8.4, C(5)*H*), 4.51 (1H, d, AB system, J_{BA} 14.6, CH$_A$$H_B$Ph), 2.87 (1H, dd, ABX system, J_{AB} 16.3, J_{AX} 7.8, C(4)H_AH$_B$) and 2.71 (1H, dd, ABX system, J_{BA} 16.3, J_{BX} 8.9, C(4)H$_A$$H_B$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.4 (*C*(3)O), 135.8 (*C*Ar$_{ipso}$), 135.7 (*C*Ar$_{ipso}$), 128.87 (*C*Ar), 128.85 (*C*Ar), 128.5 (*C*Ar), 128.3 (*C*Ar), 128.0 (*C*Ar), 126.5 (*C*Ar), 58.2 (*C*(5)H), 48.1 (*C*H$_2$Ph) and 39.3 (*C*(4)H$_2$); ***m/z*** (CI) 253.2 (100, $[M+H]^+$); HRMS (ESI^+) $C_{16}H_{17}N_2O$ ($[M+H]^+$) requires 253.1335, found 253.1333 (–0.9 ppm).

(*RS*)-2-Benzyl-5-*iso*-propylpyrazolidin-3-one 92



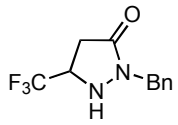
92

To a solution of (*RS*)-*tert*-butyl 2-benzyl-5-*iso*-propyl-3-oxopyrazolidine-1-carboxylate **89** (390 mg, 1.67 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.500 mL, 6.47 mmol) and the resulting solution stirred overnight at rt. TLC analysis of the crude reaction mixture showed incomplete reaction. Hence, further trifluoroacetic acid (0.200 mL, 1.62 mmol) was added and the mixture stirred for 2 h before being concentrated *in vacuo*. The resulting material was partitioned between dichloromethane (50 mL) and saturated sodium hydrogen carbonate solution (50 mL). The aqueous layer was washed with dichloromethane (2 x 50 mL) and the combined organic layers washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was then purified by column chromatography, eluting with 50 % ethyl acetate in petrol to give the title compound as a clear yellow oil which solidified on standing (179 mg, 67 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3178 (N-H), 3061 (Ar-H), 3035 (Ar-H), 2961 (C-H), 2954 (C-H), 2880 (N-C-H), 1661 (C=O), 1602 (Ar C=C) and 1560 (N-H bend); ***mp*** 53–54 ºC; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.37–7.27 (5H, m, Ar*H*), 4.64 (1H, d, AB system, J_{AB} 14.5, CH_AH$_B$Ph), 4.52 (1H, d, AB system, J_{BA} 14.5, CH$_A$$H_B$Ph), 4.07 (1H, br s, N(1)*H*), 3.22 (1H, app q, *J* 8.1, C(5)*H*), 2.61 (1H, dd, ABX system, J_{AB} 16.4, J_{AX} 7.7, C(4)H_AH$_B$), 2.34 (1H, d, ABX system, J_{BA} 16.4, J_{BX}

8.7, C(4)H$_A$*H$_B$*), 1.61 (1H, dsept, *J* 7.8, 6.7, C(5)HC*H*), 0.91 (3H, d, *J* 6.7, CH(C*H$_3$*)$_A$(CH$_3$)$_B$) and 0.89 (3H, d, *J* 6.7, CH(CH$_3$)$_A$(C*H$_3$*)$_B$); ***δ$_C$*** (75 MHz, CDCl$_3$) 172.1 (*C*(3)O), 136.1 (Ar$_{ipso}$), 128.9 (*C*Ar), 128.4 (*C*Ar), 127.9 (*C*Ar), 61.3 (*C*(5)H), 48.1 (*C*H$_2$Ph), 37.0 (*C*(4)H$_2$), 32.2 (C(5)H*C*H) and 19.2 (CH(*C*H$_3$)$_2$); ***m/z*** (CI) 219.3 (100, [M+H]$^+$); HRMS (EI) C$_{13}$H$_{18}$N$_2$O ([M]$^+$) requires 218.1414, found 218.1413 (–0.3 ppm).

(*RS*)-2-Benzyl-5-(trifluoromethyl)pyrazolidin-3-one 93



93

A solution of (*RS*)-*tert*-butyl 3-oxo-5-(trifluoromethyl)pyrazolidine-1-carboxylate **87** (1.00 g, 3.94 mmol) in DMF (8 mL) was treated with benzyl bromide (0.50 mL, 3.95 mmol) and potassium carbonate (544 mg, 3.95 mmol) and the suspension stirred at rt for 2 days. The reaction mixture was partitioned between diethyl ether (100 mL) and water (100 mL) and the resultant aqueous layer washed with further diethyl ether (2 x 100 mL). The combined organic layers were washed with brine (150 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give crude (*RS*)-*tert*-butyl 2-benzyl-5-(trifluoromethyl)-3-oxopyrazolidine-1-carboxylate **90** (1.27 g) as a clear yellow oil. Product was used without further purification. An analytical sample was taken and purified by column chromatography, eluting with 15 % ethyl acetate in petrol, to give the title compound as a clear oil which became a colourless solid on standing.

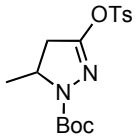
ν$_{max}$ (KBr disc)/ cm^{-1} 3064 (Ar-H), 3014 (Ar-H), 2985 (C-H), 1730 (C=O) and 1700 (C=O); ***mp*** 58–59 ºC; ***δ$_F$*** (282 MHz, CDCl$_3$) −79.0 (3F, d, *J* 7.3, C*F$_3$*); ***δ$_H$*** (300 MHz, CDCl$_3$) 7.32–7.27 (5H, m, Ar*H*), 5.19 (1H, d, AB system, *J*$_{AB}$ 14.3, C*H$_A$*H$_B$Ph), 4.77 (1H, dqd, *J* 10.1, 7.3, 1.6, C(5)*H*), 4.58 (1H, d, AB system, *J*$_{BA}$ 14.3, CH$_A$*H$_B$*Ph), 3.06 (1H, dd, *J* 17.5, 10.1, C(4)*H$_A$*H$_B$), 2.50 (1H, d, *J* 17.5, 1.6, C(4)H$_A$*H$_B$*) and 1.53 (9H, s, C(C*H$_3$*)$_3$); ***δ$_C$*** (75 MHz, CDCl$_3$) 168.5 (*C*(3)O), 155.5 (*C*(O)O), 134.4 (*C*Ar$_{ipso}$), 129.8 (*C*Ar), 128.4 (*C*Ar), 128.3 (*C*Ar), 123.3 (q, *J* 281, *C*F$_3$), 84.6 (*C*(CH$_3$)$_3$), 56.9 (q, *J* 33.8, *C*(5)H), 50.0 (*C*H$_2$Ph), 30.8 (*C*(4)H$_2$) and 28.2 (C(*C*H$_3$)$_3$); ***m/z*** HRMS (ESI$^+$) C$_{16}$H$_{20}$F$_3$N$_2$O$_3$ ([M+H]$^+$) requires 345.1421, found 345.1425 (+1.3 ppm).

Crude (*RS*)-*tert*-butyl 2-benzyl-5-(trifluoromethyl)-3-oxopyrazolidine-1-carboxylate **90** (1.04 g, 3.02 mmol) was stirred at rt overnight in a 1:2 mixture of trifluoroacetic acid/dichloromethane (15 mL) before being concentrated *in vacuo.* The resulting material was partitioned between dichloromethane (100 mL) and saturated sodium hydrogen carbonate solution (100 mL). The

aqueous layer was washed with dichloromethane (2 x 100 mL) and the combined organic layers washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was then purified by recrystallisation from diethyl ether and the minimum quantity of dichloromethane to give the title compound as a colourless solid (484 mg, 50 %).

$C_{11}H_{11}F_3N_2O$ requires C, 54.1; H 4.5; N, 11.5 %; found C 53.9; H, 4.3; N, 11.6 %; $\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3219 (N-H), 3068 (Ar-H), 3029 (Ar-H), 2951 (C-H), 2916 (C-H), 1700 (C=O) and 1667 (C=O); ***mp*** 85–86 ºC; $\boldsymbol{\delta}_F$ (282 MHz, $CDCl_3$) −79.1 (3F, d, *J* 7.2, C*F*$_3$); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.38–7.28 (5H, m, Ar*H*), 4.92 (1H, d, AB system, J_{AB} 14.6, CH_AH$_B$Ph), 4.69 (1H, s, N(1)*H*), 4.25 (1H, d, AB system, J_{BA} 14.6, CH$_A$$H_B$Ph), 3.93 (1H, dqd, *J* 10.0, 7.2, 3.3, C(5)*H*), 2.96 (1H, dd, *J* 17.4, 10.0, C(4)H_AH$_B$) and 2.66 (1H, d, *J* 17.4, 3.3, C(4)H$_A$$H_B$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 168.3 (*C*(3)O), 135.1 (*C*Ar$_{ipso}$), 129.0 (*C*Ar), 128.6 (*C*Ar), 128.3 (*C*Ar), 124.7 (q, *J* 279, *C*F$_3$), 54.0 (q, *J* 32.3, *C*(5)H), 48.5 (*C*H$_2$Ph) and 31.9 (*C*(4)H$_2$); ***m/z*** HRMS (ESI^+) $C_{11}H_{12}F_3N_2O$ ($[M+H]^+$) requires 245.0896, found 245.0890 (+0.7 ppm).[1]

(*RS*)-*tert*-Butyl 5-methyl-3-(tosyloxy)-4,5-dihydro-1*H*-pyrazole-1-carboxylate 96

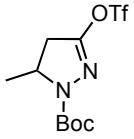


96

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (0.991 g, 4.95 mmol) triethylamine (0.800 mL, 5.74 mmol) and tosyl chloride (1.00 g, 5.25 mmol) were combined according to general procedure A. The crude material was then purified by column chromatography, eluting with 15 % ethyl acetate in petrol to give the title compound as a colourless oil which solidified on standing (810 mg, 46 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 2987 (C-H), 2934 (C-H), 1698 (C=O), 1645 (C=N), 1596 (Ar C=C) and 1586 (Ar C=C); ***mp*** 84–86 ºC; $\boldsymbol{\delta_N}$ ($CDCl_3$) 295 (*N*(2)COS(O)$_2$), 156 (*N*(1)Boc); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8.4, Ar*H*), 7.36 (2H, d, *J* 8.4, Ar*H*), 4.46 (1H, app dquin, *J* 11.0. 6.1, C(5)*H*), 3.26 (1H, dd, ABX system, J_{AB} 17.8, J_{AX} 11.0, C(4)H_AH$_B$), 2.61 (1H, dd, ABX system, J_{BA} 17.8, J_{BX} 5.3, C(4)H$_A$$H_B$), 1.49 (9H, s, C(C$H_3$)$_3$) and 1.34 (3H, d, *J* 6.3, C(5)HCH_3); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 155.0 (*C*(O)O), 151.9 (*C*(4)N), 146.3 (*C*Ar$_{ipso}$), 132.3(*C*Ar$_{para}$), 129.9 (*C*Ar), 129.3 (*C*Ar), 81.3 (*C*(CH$_3$)$_3$), 55.5 (*C*(5)H), 39.0 (*C*(4)H$_2$), 28.4 (C(*C*H$_3$)$_3$), 21.9 (CAr$_{para}$*C*H$_3$) and 20.7 (C(5)H*C*H$_3$); ***m/z*** (ESI^+) 372.2 (100, $[M+NH_4]^+$); HRMS (ESI^+) $C_{16}H_{26}N_3O_5S$ ($[M+NH_4]^+$) requires 372.1588, found 372.1593 (+1.4 ppm).

(*RS*)-*tert*-Butyl 3-(trifluoromethylsulfonyloxy)-5-methyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate 97

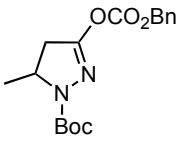


97

To a solution of (*RS*)-*tert*-butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (250 mg, 1.25 mmol) in dichloromethane (5 mL) was added triethylamine (0.700 mL, 5.00 mmol). The resulting suspension was then cooled to −78 ºC and triflic anhydride (0.410 mL, 2.50 mmol) added dropwise. The reaction mixture was stirred at −78 ºC for 2 h and 1:1 water-methanol added (4 mL). The reaction mixture was warmed to rt, maintained for 30 min, then diluted with diethyl ether (30 mL). The organic layer was washed with 0.1 M hydrochloric acid (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was then purified by column chromatography, eluting with 10 % ethyl acetate in petrol to give the title compound as a colourless oil which solidified on standing (176 mg, 42 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 2990 (C-H), 2932 (C-H), 2873 (N-C-H), 1713 (C=O), 1635 (C=N) and 1572 (Ar C=C); ***mp*** 41–43 ºC; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.61 (1H, app dquin, *J* 11.3. 6.3, C(5)*H*), 3.38 (1H, dd, ABX system, J_{AB} 17.8, J_{AX} 11.3, C(4)H_AH_B), 2.70 (1H, dd, ABX system, J_{BA} 17.8, J_{BX} 5.3, C(4)H_AH_B), 1.52 (9H, s, C(CH_3)$_3$) and 1.42 (3H, d, *J* 6.3, C(5)HCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 153.2 (*C*(O)O), 151.6 (*C*(4)N), 118.5 (q, *J* = 321, *C*F_3), 82.4 (*C*$(CH_3)_3$), 56.9 (*C*(5)H), 38.7 (*C*(4)H_2), 28.4 (C(*C*H_3)$_3$) and 20.8 (C(5)H*C*H_3); ***m/z*** (CI) 132.3 (100, $[SO_2CF_3]^+$), 350.3 (20, $[M+NH_4]^+$); HRMS (ESI^+) $C_{10}H_{19}F_3N_3O_5S$ ($[M+NH_4]^+$) requires 350.0992, found 350.0991 (–0.3 ppm).

(*RS*)-*tert*-Butyl 3-(benzyloxycarbonyloxy)-5-methyl-4,5-dihydro-1H-pyrazole-1-carboxylate 98



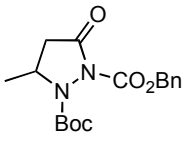
98

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (1.00 g, 5.00 mmol), triethylamine (0.800 mL, 5.74 mmol) and benzyl chloroformate (0.75 mL, 5.25 mmol) were combined according to general procedure A to give crude product (1.77 g). Attempted

purification of this material by column chromatography led to decomposition and return of starting compound **72**. Hence, characterisation was carried out on the crude mixture.

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3066 (Ar-H), 3035 (Ar-H), 2978 (C-H), 2932 (C-H), 2863 (N-C-H), 1751 (C=O), 1725 (C=O), 1648 (C=N) and 1587 (Ar C=C); $\boldsymbol{\delta_N}$ ($CDCl_3$) 296 (*N*(2)COC(O)), 155 (*N*(1)Boc); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.40–7.33 (5H, m, Ar*H*), 5.23 (2H, s, CH_2Ph), 4.54 (1H, app dquin, *J* 11.1. 6.1, C(5)*H*), 3.37 (1H, dd, ABX system, J_{AB} 17.7, J_{AX} 11.1, C(4)H_AH$_B$), 2.68 (1H, dd, ABX system, J_{BA} 17.7, J_{BX} 5.0, C(4)H$_A$$H_B$), 1.52 (9H, s, C(C$H_3$)$_3$) and 1.39 (3H, d, *J* 6.3, C(5)HCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 156.3 (*C*(4)N), 151.2 (O*C*(O)O), 134.1 (*C*Ar$_{ipso}$), 129.2 (*C*Ar), 128.9 (*C*Ar), 128.7 (*C*Ar), 81.6 (*C*(CH$_3$)$_3$), 71.2 (*C*H$_2$Ph), 56.0 (*C*(5)H), 38.1 (*C*(4)H$_2$), 28.5 (C(*C*H$_3$)$_3$) and 20.7 (C(5)H*C*H$_3$); ***m/z*** (ESI^+) 357.0 (100, $[M+Na]^+$); HRMS (ESI^+) $C_{17}H_{22}N_2NaO_5$ ($[M+Na]^+$) requires 357.1426, found 357.1419 (–2.1 ppm).

(*RS*)-1-Benzyl 2-*tert*-butyl 3-methyl-5-oxopyrazolidine-1,2-dicarboxylate 99

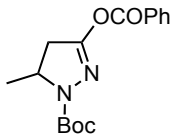


99

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (1.01 g, 5.04 mmol), sodium hydride (220 mg, 5.50 mmol) and benzyl chloroformate (0.75 mL, 5.25 mmol) were combined according to general procedure B. The crude material was then purified by column chromatography, eluting with 25 % ethyl acetate in petrol to give the title compound as a colourless oil (684 mg, 41 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3066 (Ar-H), 3034 (Ar-H), 2979 (C-H), 2933 (C-H), 2874 (N-C-H), 1799 (C=O), 1751 (C=O), 1728 (C=O) and 1587 (Ar C=C); $\boldsymbol{\delta_N}$ ($CDCl_3$) 166 (*N*(2)CO_2Bn), 137 (*N*(1)Boc); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.45–7.28 (5H, m, Ar*H*), 5.36 (1H, d, AB system, J_{AB} 12.3, CH_AH$_B$Ph), 5.26 (1H, d, AB system, J_{BA} 12.3, CH$_A$$H_B$Ph), 4.42 (1H, app quin, *J* 7.0, C(5)*H*), 2.97 (1H, dd, *J* 17.1, 8.0, C(4)H_AH$_B$), 1.96 (1H, d, *J* 17.1, C(4)H$_A$$H_B$), 1.38 (9H, s, C(C$H_3$)$_3$) and 1.31 (3H, d, *J* 6.8, C(5)HCH_3); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 169.9 (*C*(3)O), 155.8 (N(1)*C*(O)O), 149.7 (N(2)*C*(O)O), 135.0 (*C*Ar$_{ipso}$), 128.7 (*C*Ar), 128.6 (*C*Ar), 128.4 (*C*Ar), 83.6 (*C*(CH$_3$)$_3$), 68.9 (*C*H$_2$Ph), 53.6 (*C*(5)H), 39.6 (*C*(4)H$_2$), 28.0 (C(*C*H$_3$)$_3$) and 19.9 (C(5)H*C*H$_3$); ***m/z*** (CI) 235.1 (100, $[M–Boc+2H]^+$), 352.2 (96, $[M+NH_4]^+$); HRMS (ESI^+) $C_{17}H_{26}N_3O_5$ ($[M+NH_4]^+$) requires 352.1867, found 352.1872 (+1.4 ppm).

(*RS*)-*tert*-Butyl 3-(benzoyloxy)-5-methyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate 100

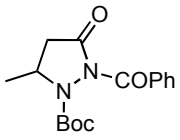


100

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (250 mg, 1.25 mmol) triethylamine (0.200 mL, 1.38 mmol) and benzoyl chloride (0.200 mL, 1.73 mmol) were combined according to general procedure A to give crude product (568 mg). Attempted purification of this material by column chromatography led to decomposition to unidentified side-products. Hence, characterisation was carried out on the crude mixture.

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3065 (Ar-H), 2979 (C-H), 2932 (C-H), 2862 (N-C-H), 1750 (C=O), 1642 (C=O) and 1601 (C=N); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 8.11–8.07 (2H, m, Ar*H*), 7.56–7.45 (3H, m, Ar*H*), 4.59 (1H, app dquin, *J* 11.0. 6.0, C(5)*H*), 3.50 (1H, dd, ABX system, J_{AB} 17.6, J_{AX} 11.0, C(4)H_AH_B), 2.83 (1H, dd, ABX system, J_{BA} 17.6, J_{BX} 4.9, C(4)H_AH_B), 1.54 (9H, s, C(CH_3)$_3$) and 1.45 (3H, d, *J* 6.3, C(5)HCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 163.2 (*C*(O)Ph), 157.3 (*C*(4)N), 134.6 (*C*Ar$_{ipso}$), 130.6 (*C*Ar), 130.5 (*C*Ar), 128.8 (*C*Ar), 81.5 (*C*(CH_3)$_3$), 55.8 (*C*(5)H), 38.7 (*C*(4)H_2), 28.4 (C(*C*H_3)$_3$) and 20.6 (C(5)H*C*H_3); ***m/z*** (ESI^+) 327.1 (100, $[M+Na]^+$); HRMS (ESI^+) $C_{16}H_{20}N_2NaO_4$ ($[M+Na]^+$) requires 327.1321, found 327.1323 (+0.6 ppm).

(*RS*)-*tert*-Butyl 2-benzoyl-5-methyl-3-oxopyrazolidine-1-carboxylate 101



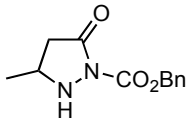
101

(*RS*)-*tert*-Butyl 5-methyl-3-oxopyrazolidine-1-carboxylate **72** (988 mg, 4.93 mmol), sodium hydride (225 mg, 5.63 mmol) and benzoyl chloride (0.60 mL, 5.24 mmol) were combined according to general procedure B. The resulting material was dissolved in toluene (15 mL) and refluxed for 5 h. The crude material was then purified by column chromatography, eluting with 25 % ethyl acetate in petrol to give the title compound as a colourless solid (685 mg, 45 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 2984 (C-H), 2932 (C-H), 2863 (N-C-H), 1759 (C=O), 1727 (C=O), 1699 (C=O) and 1596 (Ar C=C); ***mp*** 129–132 ºC; $\boldsymbol{\delta_N}$ ($CDCl_3$) 184 (*N*(2)C(O)), 136 (*N*(1)Boc); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.81 (2H, dd, *J* 8.4, 1.3, ArH_{ortho}), 7.57 (1H, app tt, *J* 7.9, 1.3, ArH_{para}), 7.48–7.40 (2H, m, ArH_{meta}), 4.78 (1H, app quin, *J* 7.1, C(5)*H*), 3.14 (1H, dd, *J* 16.9, 8.3,

C(4)H_AH$_B$), 2.28 (1H, d, *J* 16.9, C(4)H$_A$$H_B$), 1.40 (9H, s, C(C$H_3$)$_3$) and 1.39 (3H, d, *J* 6.4, C(5)HCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 170.8 (*C*(3)O), 166.6 (*C*(O)Ph), 154.5 (*C*(O)O), 133.2 (*C*Ar$_{ipso}$), 133.1 (*C*Ar), 130.0 (*C*Ar), 128.2 (*C*Ar), 83.5 (*C*(CH$_3$)$_3$), 52.7 (*C*(5)H), 39.9 (*C*(4)H$_2$), 28.2 (C(*C*H$_3$)$_3$) and 20.4 (C(5)H*C*H$_3$); ***m/z*** (ESI^+) 139.2 (100, $[H_2NC(O)Ph+NH_4]^+$), 305.2 (15, $[M+H]^+$), 322.3 (20, $[M+NH_4]^+$); HRMS (ESI^+) $C_{16}H_{24}N_3O_4$ ($[M+NH_4]^+$) requires 322.1761, found 322.1761.

(*RS*)-Benzyl 3-methyl-5-oxopyrazolidine-1-carboxylate 102

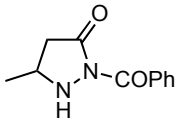


102

To a solution of (*RS*)-1-benzyl 2-*tert*-butyl 3-methyl-5-oxopyrazolidine-1,2-dicarboxylate **99** (560 mg, 1.67 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.600 mL, 8.09 mmol) and the resulting solution stirred overnight at rt. TLC analysis of the crude reaction mixture showed incomplete reaction. Hence, further trifluoroacetic acid (0.120 mL, 1.62 mmol) was added and the mixture stirred for 4 h before being concentrated *in vacuo*. The resulting material was partitioned between dichloromethane (30 mL) and saturated sodium hydrogen carbonate solution (30 mL). The aqueous layer was washed with dichloromethane (2 x 30 mL) and the combined organic layers washed with brine (90 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was then purified by column chromatography, eluting with ethyl acetate to give the title compound as a colourless oil (304 mg, 78 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3234 (N-H), 2972 (C-H), 2927 (C-H), 1783 (C=O), 1729 (C=O), 1638 (N-H bend) and 1583 (Ar C=C); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.47–7.42 (2H, m, Ar*H*), 7.40–7.31 (3H, m, Ar*H*), 5.34 (1H, d, AB system, J_{AB} 12.3, CH_AH$_B$Ph), 5.27 (1H, d, AB system, J_{BA} 12.3, CH$_A$$H_B$Ph), 4.56 (1H, d, *J* 9.9, N(1)*H*), 3.71 (1H, app tquin, *J* 9.7, 6.5, C(5)*H*), 2.75 (1H, dd, ABX system, J_{AB} 16.9, J_{AX} 6.7, C(4)H_AH$_B$), 2.37 (1H, dd, ABX system, J_{BA} 16.9, J_{BX} 9.7, C(4)H$_A$$H_B$) and 1.31 (3H, d, *J* 6.4, C(5)HCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 172.1 (*C*(3)O), 150.0 (N(2)*C*(O)O), 135.1 (*C*Ar$_{ipso}$), 128.7 (*C*Ar), 128.6 (*C*Ar), 128.5 (*C*Ar), 68.6 (*C*H$_2$Ph), 50.9 (*C*(5)H), 41.9 (*C*(4)H$_2$) and 18.4 (C(5)H*C*H$_3$); ***m/z*** (CI) 257.0 (100, $[M+H]^+$); HRMS (ESI^+) $C_{12}H_{14}N_2NaO_3$ ($[M+Na]^+$) requires 257.0902, found 257.0910 (+3.2 ppm).

(*RS*)-2-Benzoyl-5-methylpyrazolidin-3-one 103

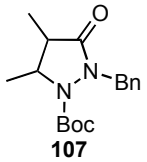


103

To a solution of (*RS*)-*tert*-butyl 2-benzoyl-5-methyl-3-oxopyrazolidine-1-carboxylate **101** (457 mg, 1.50 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.600 mL, 8.10 mmol) and the resulting solution stirred overnight at rt before being concentrated *in vacuo*. The resulting material was partitioned between dichloromethane (40 mL) and saturated sodium hydrogen carbonate solution (40 mL). The aqueous layer was washed with dichloromethane (2 x 40 mL) and the combined organic layers washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a clear yellow oil (263 mg, 86 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3224 (N-H), 3061 (Ar-H), 3029 (Ar-H), 2974 (C-H), 2931 (C-H), 2873 (N-C-H), 1757 (C=O), 1672 (C=O), 1631 (N-H bend), 1600 (Ar C=C) and 1579 (Ar C=C); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.65 (2H, dd, *J* 8.3, 1.3, ArH_{ortho}), 7.54 (1H, app tt, *J* 7.5, 1.3, ArH_{para}), 7.45–7.39 (2H, m, ArH_{meta}), 5.19 (1H, d, *J* 8.3, N(1)*H*), 3.84 (1H, app tquin, *J* 9.1, 6.4, C(5)*H*), 2.85 (1H, dd, ABX system, J_{AB} 17.1, J_{AX} 6.8, C(4)H_AH$_B$), 2.50 (1H, dd, ABX system, J_{BA} 17.1, J_{BX} 9.5, C(4)H$_A$$H_B$) and 1.40 (3H, d, *J* 6.3, C(5)HCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.9 (*C*(3)O), 166.7 (*C*(O)Ph), 133.1 (*C*Ar$_{ipso}$), 132.4 (*C*Ar), 129.4 (*C*Ar), 128.0 (*C*Ar), 50.2 (*C*(5)H), 42.1 (*C*(4)H_2) and 18.8 (C(5)H*C*H$_3$); ***m/z*** (CI) 205.1 (100, $[M+H]^+$); HRMS (CI) $C_{11}H_{13}N_2O_2$ ($[M+H]^+$) requires 205.0977, found 205.0978 (+0.5 ppm).

(*RS*)-*tert*-Butyl 2-benzyl-4,5-dimethyl-3-oxopyrazolidine-1-carboxylate 107



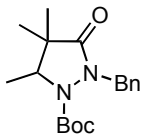
107

To a solution of (*RS*)-*tert*-butyl 2-benzyl-5-methyl-3-oxopyrazolidine-1-carboxylate **74** (345 mg, 1.19 mmol) in THF (5 mL), cooled to –78 ºC, was added KHMDS (0.46 M in toluene, 3.10 mL, 1.43 mmol) and the red solution stirred for 90 min before it was treated with iodomethane (0.220 mL, 3.57 mmol). The mixture was stirred at –78 ºC for 3 h and then quenched with pH 7 phosphate buffer solution (20 mL), before being warmed to rt. The

biphasic solution was extracted with diethyl ether (3 x 15 mL) and the combined organic extracts washed with brine (30 mL) and dried ($MgSO_4$) before being filtered through a plug of silica gel and concentrated *in vacuo*. The crude material was purified by column chromatography, eluting with 15 then 25 % ethyl acetate in petrol to give the product as a colourless oil (75 mg, 21 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3065 (Ar-H), 3032 (Ar-H), 2976 (C-H), 2931 (C-H), 2873 (N-C-H), 1745-1667 (2 x C=O), 1604 (Ar C=C) and 1586 (Ar C=C); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.24-7.20 (5H, m, Ar*H*), 5.18 (1H, d, AB system, J_{AB} 14.2, CH_AH_BPh), 4.31 (1H, d, AB system, J_{BA} 14.2, CH_AH_BPh), 3.95 (1H, q, *J* 6.8, C(5)*H*), 1.98 (1H, q, *J* 7.4, C(4)*H*), 1.47 (9H, s, $C(CH_3)_3$), 1.15 (3H, d, *J* 7.4, C(4)HCH_3) and 0.55 (3H, d, *J* 6.8, C(5)HCH_3); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 174.9 (*C*(3)O), 157.6 (*C*(O)O), 136.1 (*C*Ar_{ipso}), 130.0 (*C*Ar), 128.7 (*C*Ar), 128.5 (*C*Ar), 82.8 ($C(CH_3)_3$), 61.8 (*C*(5)H), 49.0 (CH_2Ph), 45.4 (*C*(4)H), 28.6 ($C(CH_3)_3$), 19.1 (C(5)HCH_3) and 15.8 (C(4)HCH_3); ***m/z*** (CI) 305.3 (100, $[M+H]^+$); HRMS (ESI^+) $C_{17}H_{25}N_2O_3$ ($[M+H]^+$) requires 305.1860, found 305.1860 (+0.2 ppm).

(*RS*)-*tert*-Butyl 2-benzyl-4,4,5-trimethyl-3-oxopyrazolidine-1-carboxylate 108



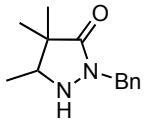
108

To a solution of (*RS*)-*tert*-butyl 2-benzyl-5-methyl-3-oxopyrazolidine-1-carboxylate **74** (268 mg, 0.923 mmol) in THF (5 mL), cooled to −78 ºC, was added KHMDS (0.46 M in toluene, 10.0 mL, 4.60 mmol) and the red solution stirred for 70 min before treatment with iodomethane (0.570 mL, 9.23 mmol). The mixture was stirred at −78 ºC for 90 min, then at rt for 60 min. The reaction was then quenched with pH 7 phosphate buffer solution (20 mL), the resulting biphasic solution extracted with diethyl ether (3 x 15 mL) and the combined organic extracts washed with brine (30 mL) and dried ($MgSO_4$) before being filtered through a plug of silica gel and concentrated *in vacuo*. ^1H NMR showed a mixture of starting material **74**, monomethylated material and product **108** in the ratio 27:44:29 and so the crude material was redissolved in THF (5 mL), cooled to −78 ºC and treated, as before, with identical amounts of KHMDS and iodomethane. The mixture was stirred at −78 ºC for 60 min before being quenched and following of the work-up procedure previously described. The crude material was purified by column chromatography, eluting with 10 % ethyl acetate in petrol to give the product as a

colourless oil (75 mg, 26 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3065 (Ar-H), 3032 (Ar-H), 2978 (C-H), 2934 (C-H), 2871 (N-C-H), 1747–1674 (2 x C=O) and 1605 (Ar C=C); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.24–7.20 (5H, m, Ar*H*), 5.15 (1H, d, AB system, J_{AB} 14.2, CH_AH_BPh), 4.31 (1H, d, AB system, J_{BA} 14.2, CH_AH_BPh), 3.99 (1H, q, *J* 6.9, C(5)*H*), 1.48 (9H, s, $C(CH_3)_3$), 1.09 (3H, s, $C(4)(CH_3)_A(CH_3)_B$), 0.92 (3H, s, $C(4)(CH_3)_A(CH_3)_B$) and 0.42 (3H, d, *J* 6.9, C(5)HCH_3); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 176.6 (*C*(3)O), 157.3 (*C*(O)O), 136.2 (CAr_{ipso}), 130.2 (*C*Ar), 128.8 (*C*Ar), 128.5 (*C*Ar), 82.7 ($C(CH_3)_3$), 65.3 (*C*(5)H), 49.1 (CH_2Ph), 44.6 ($C(4)(CH_3)_2$), 28.7 ($C(CH_3)_3$), 24.8 (C(5)HCH_3), 18.2 ($C(4)(CH_3)_A(CH_3)_B$) and 15.8 ($C(4)(CH_3)_A(CH_3)_B$); ***m/z*** (CI) 219.2 (100, $[M-Boc+2H]^+$), 319.3 (60, $[M+H]^+$); HRMS (ESI^+) $C_{18}H_{27}N_2O_3$ ($[M+H]^+$) requires 319.2016, found 319.2015 (+0.2 ppm).

(*RS*)-2-Benzyl-4,4,5-trimethylpyrazolidin-3-one 109



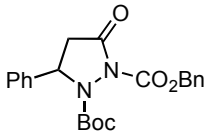
109

To a solution of (*RS*)-*tert*-butyl 2-benzyl-4,4,5-trimethyl-3-oxopyrazolidine-1-carboxylate **108** (142 mg, 0.446 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.2 mL, 2.69 mmol) and the resulting solution stirred overnight at rt. TLC analysis of the crude reaction mixture showed incomplete reaction. Hence, further trifluoroacetic acid (0.2 mL, 2.69 mmol) was added and the mixture stirred for 2 h before being concentrated *in vacuo*. The resulting material was partitioned between dichloromethane (20 mL) and saturated sodium hydrogen carbonate solution (20 mL). The aqueous layer was washed with dichloromethane (2 x 20 mL) and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (94 mg, 96 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3202 (N-H), 3064 (Ar-H), 3032 (Ar-H), 2969 (C-H), 2930 (C-H), 2873 (N-C-H), 1678 (C=O), 1606 (Ar C=C) and 1587 (N-H bend); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.37–7.24 (5H, m, Ar*H*), 4.82 (1H, d, AB system, J_{AB} 14.7, CH_AH_BPh), 4.34 (1H, d, AB system, J_{BA} 14.7, CH_AH_BPh), 3.76 (1H, br s, N(1)*H*), 3.24 (1H, q, *J* 6.6, C(4)HCH_3), 1.15 (3H, s, $C(4)(CH_3)_A(CH_3)_B$), 1.06 (3H, d, *J* 6.6, C(5)HCH_3) and 0.95 (3H, s, $C(4)(CH_3)_A(CH_3)_B$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 177.7 (*C*(3)O), 136.2 (CAr_{ipso}), 128.9 (*C*Ar), 128.2 (*C*Ar), 127.9 (*C*Ar), 61.4 (*C*(5)H), 48.1 (CH_2Ph), 43.5 ($C(4)(CH_3)_2$), 21.7 ($C(4)(CH_3)_A(CH_3)_B$),

16.4 (C(4)$(CH_3)_A(CH_3)_B$) and 12.0 (C(5)HCH_3); ***m/z*** (ESI^+) 241.1 (100, $[M+Na]^+$); HRMS (ESI^+) $C_{13}H_{18}N_2ONa$ ($[M+Na]^+$) requires 241.1317, found 241.1317.

(*RS*)-1-Benzyl 2-*tert*-butyl 5-oxo-3-phenylpyrazolidine-1,2-dicarboxylate 112

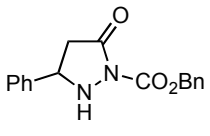


112

(*RS*)-1-Benzyl 2-*tert*-butyl 5-oxo-3-phenylpyrazolidine-1,2-dicarboxylate **85** (3.15 g, 12.1 mmol), sodium hydride (530 mg, 13.3 mmol) and benzyl chloroformate (1.81 mL, 12.7 mmol) were combined according to general procedure B. The resulting material was taken up in toluene (40 mL) and refluxed for 4 h before concentration *in vacuo*. The crude material was then purified by column chromatography, eluting with 15 then 25 % ethyl acetate in petrol to give the title compound as a clear yellow oil which became a colourless solid on trituration with petrol (1.83 g, 38 %).

ν_{max} (KBr disc)/ cm^{-1} 3064 (Ar-H), 3025 (Ar-H), 2982 (C-H), 1795 (C=O), 1733 (2 x C=O) and 1560 (Ar C=C); ***mp*** 112–114 ºC; ***δ_N*** ($CDCl_3$) 169 (*N*(2)CO_2Bn), 133 (*N*(1)Boc); ***δ_H*** (500 MHz, $CDCl_3$) 7.44–7.28 (10H, m, Ar*H*), 5.70 (1H, d, *J* 8.6, C(5)*H*), 5.36 (1H, d, AB system, J_{AB} 12.3, C$H_A$$H_B$Ph), 5.30 (1H, d, AB system, J_{BA} 12.3, C$H_A$$H_B$Ph), 3.35 (1H, dd, *J* 17.2, 8.6, C(4)$H_A$$H_B$), 2.79 (1H, d, *J* 17.2, C(4)$H_A$$H_B$) and 1.43 (9H, s, C(C$H_3$)$_3$); ***$\delta_C$*** (100 MHz, $CDCl_3$) 169.2 (*C*(3)O), 155.8 (N(1)*C*(O)O), 149.2 (N(2)*C*(O)O), 138.4 (*C*Ar_{ipso}), 134.9 (*C*Ar_{ipso}), 129.1 (*C*Ar), 128.7 (*C*Ar), 128.6 (*C*Ar), 128.4 (*C*Ar), 128.2 (*C*Ar), 125.6 (*C*Ar), 84.1 (*C*$(CH_3)_3$), 69.0 (*C*H_2Ph), 59.7 (*C*(5)H), 40.1 (*C*(4)H_2) and 28.0 (C(*C*H_3)$_3$); ***m/z*** HRMS (ESI^+) $C_{22}H_{24}N_2NaO_5$ ($[M+Na]^+$) requires 419.1577, found 419.1585 (+1.8 ppm).

(*RS*)-Benzyl 5-oxo-3-phenylpyrazolidine-1-carboxylate 114



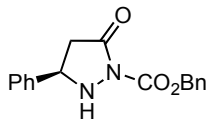
114

To a solution of (*RS*)-1-benzyl-2-*tert*-butyl 5-oxo-3-phenylpyrazolidine-1,2-dicarboxylate **112** (1.60g, 4.04 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (1.50 mL, 19.7 mmol) and the resulting solution stirred overnight at rt before being concentrated *in vacuo.* The resulting material was partitioned between dichloromethane (60 mL) and saturated sodium

hydrogen carbonate solution (60 mL). The aqueous layer was washed with dichloromethane (2 x 60 mL) and the combined organic layers washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by recrystallisation from petrol and the minimum quantity of dichloromethane to give the title compound as colourless needles (816 mg, 68 %).

$C_{17}H_{16}N_2O_3$ requires C, 68.9; H 5.4; N, 9.5 %; found C 68.6; H, 5.2; N, 9.5 %; $\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3226 (N-H), 3058 (C-H), 3030 (C-H), 1739 (C=O), 1653 (N-H bend); ***mp*** 101–102 ºC; $\boldsymbol{\delta_N}$ ($CDCl_3$) 167 (*N*(2)CO_2Bn), 103 (*N*(1)H); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.49–7.43 (2H, m, Ar*H*), 7.41–7.31 (8H, m, Ar*H*), 5.37 (1H, d, AB system, J_{AB} 12.2, C$H_A$$H_B$Ph), 5.31 (1H, d, AB system, J_{BA} 12.2, C$H_A$$H_B$Ph), 4.94 (1H, bs, N(1)*H*), 4.75 (1H, app t, *J* 8.2 C(5)*H*), 3.05 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 7.3, C(4)$H_A$$H_B$) and 2.93 (1H, dd, ABX system, J_{BA} 17.0, J_{BX} 9.8, C(4)$H_A$$H_B$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 170.7 (*C*(3)O), 149.8 (N(2)*C*(O)O), 137.3 (*C*Ar$_{ipso}$), 135.1 (*C*Ar$_{ipso}$), 129.2 (*C*Ar), 128.9 (*C*Ar), 128.8 (*C*Ar), 128.7 (*C*Ar), 128.6 (*C*Ar), 126.7 (*C*Ar), 68.7 (*C*H_2Ph), 57.9 (*C*(5)H) and 41.0 (*C*(4)H_2); ***m/z*** HRMS (ESI^+) $C_{17}H_{17}N_2O_3$ ($[M+H]^+$) requires 297.1234, found 297.1237 (+1.1 ppm).

(*R*)-Benzyl 5-oxo-3-phenylpyrazolidine-1-carboxylate (*R*)-114

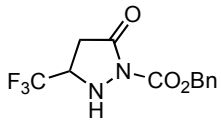


(*R*)-114

Synthesised from **(*R*)-83** by identical means to those described for racemic **83**.

$\boldsymbol{[\alpha]^{20}_D}$ +22.4 (*c* 0.25, dichloromethane); ***mp*** 123–125 ºC.

(*RS*)-Benzyl 5-oxo-3-(trifluoromethyl)pyrazolidine-1-carboxylate 115



115

(*RS*)-1-Benzyl 2-*tert*-butyl 5-oxo-3-(trifluoromethyl)pyrazolidine-1,2-dicarboxylate **113** (619 mg, 2.43 mmol), sodium hydride (107 mg, 2.68 mmol) and benzyl chloroformate (0.400 mL, 2.55 mmol) were combined according to general procedure B with a modified work-up. In this case, the reaction was quenched with water (2 mL) and concentrated *in vacuo*. The resulting material was taken up in toluene (20 mL) and refluxed for 3 h before being cooled,

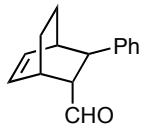
filtered and concentrated *in vacuo* to give crude product (930 mg) as a yellow oil. Product was used without further purification. An analytical sample was taken and purified by column chromatography, eluting with 10 % ethyl acetate in petrol to give the title compound as a colourless solid.

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3028 (C-H), 2984 (C-H), 1790 (C=O) and 1748 (C=O); ***mp*** 65–67 ºC; $\boldsymbol{\delta}_F$ (282 MHz, $CDCl_3$) −78.8 (3F, d, *J* 7.2, CF_3); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.43–7.32 (5H, m, Ar*H*), 5.35 (1H, d, AB system, J_{AB} 12.3, C$H_A$$H_B$Ph), 5.30 (1H, d, AB system, J_{BA} 12.3, C$H_A$$H_B$Ph), 4.42 (1H, dqd, *J* 9.5, 7.2, 1.3, C(5)*H*), 3.14 (1H, dd, *J* 18.2, 9.5, C(4)$H_A$$H_B$), 2.77 (1H, d, *J* 18.2, 1.3, C(4)$H_A$$H_B$) and 1.38 (9H, s, C(C$H_3$)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 167.1 (*C*(3)O), 154.3 (N(1)*C*(O)O), 149.9 (N(2)*C*(O)O), 134.7 (*C*Ar$_{ipso}$), 128.8 (*C*Ar), 128.7 (*C*Ar), 128.5 (*C*Ar), 123.8 (q, *J* 281, *C*F_3), 85.4 (*C*(CH_3)$_3$), 69.4 (*C*H_2Ph), 56.2 (q, *J* 33.9, *C*(5)H), 32.2 (*C*(4)H_2) and 27.9 (C(*C*H_3)$_3$); ***m/z*** HRMS (ESI^+) $C_{17}H_{23}F_3N_3O_5$ ($[M+NH_4]^+$) requires 406.1584, found 406.1588 (+0.9 ppm).

A solution of crude (*RS*)-1-benzyl-2-*tert*-butyl 5-oxo-3-(trifluoromethyl)pyrazolidine-1,2-dicarboxylate **113** (890 mg, 2.29 mmol) was stirred in a 1:2 mixture of trifluoroacetic acid/dichloromethane (15 mL) overnight at rt before being concentrated *in vacuo.* The resulting material was partitioned between dichloromethane (100 mL) and saturated sodium hydrogen carbonate solution (100 mL). The aqueous layer was washed with dichloromethane (2 x 100 mL) and the combined organic layers washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by recrystallisation from diethyl ether and the minimum quantity of dichloromethane to give the title compound as colourless needles (281 mg, 42 %).

$\boldsymbol{\nu_{max}}$ (film)/ cm^{-1} 3261 (N-H), 3014 (Ar-H), 2935 (C-H), 1760 (C=O) and 1714 (C=O); ***mp*** 90–92 ºC; $\boldsymbol{\delta}_F$ (282 MHz, $CDCl_3$) −78.5 (3F, d, *J* 7.6, CF_3); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.44–7.33 (5H, m, Ar*H*), 5.34 (1H, d, AB system, J_{AB} 12.3, C$H_A$$H_B$Ph), 5.32 (1H, d, *J* 7.9, N(1)*H*), 5.30 (1H, d, AB system, J_{BA} 12.3, C$H_A$$H_B$Ph), 4.13–3.98 (1H, m, C(5)*H*), 3.07 (1H, dd, ABX system, J_{AB} 18.1, J_{AX} 9.6, C(4)$H_A$$H_B$) and 2.84 (1H, dd, ABX system, J_{BA} 18.1, J_{BX} 4.1, C(4)$H_A$$H_B$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 168.3 (*C*(3)O), 149.5 (N(2)*C*(O)O), 135.9 (*C*Ar$_{ipso}$), 128.8 (*C*Ar), 128.4 (*C*Ar), 124.1 (q, *J* 280, *C*F_3), 68.9 (*C*H_2Ph), 53.4 (q, *J* 32.6, *C*(5)H) and 33.1 (*C*(4)H_2); ***m/z*** HRMS (ESI^+) $C_{12}H_{15}F_3N_3O_3$ ($[M+NH_4]^+$) requires 306.1090, found 306.1066 (+2.0 ppm).

endo-(1*S*,2*R*,3*R*,4*R*)-3-Phenylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde _endo_-(2*R*)-118

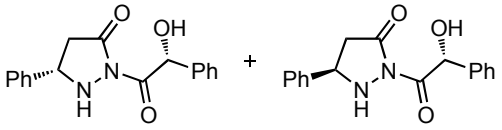


***endo*-(2*R*)-118**

(*E*)-Cinnamaldehyde **37** (60.0 μL, 0.475 mmol), triflic acid (0.190 M solution in methanol, 0.250 mL, 47.5 μmol), catalyst **170** (10 mol%, 20.0 mg, 47.5 μmol) and cyclohexadiene (140 μL, 1.43 mmol) were combined according to general procedure D. After 3 days, ^{1}H NMR spectroscopic analysis indicated reaction had achieved 51 % conversion (*exo*:*endo* 6:94) and reaction was quenched as outlined in general procedure D. The crude material was then purified by column chromatography, eluting with 7.5 % diethyl ether in petrol to yield the title compound as a colourless solid with spectroscopic data in accordance with the literature (43 mg, 43 %).[146]

[α]*$^{20}_{D}$** –35.7 (*c* 0.3, chloroform) (lit. $[\alpha]^{20}_{D}$ +82 ((1*R*,2*S*,3*S*,4*S*) enantiomer, >95 % ee, *c* 1.0, dichloromethane));[85] ***mp 54–55 ˚C; ***δ*$_H$** (300 MHz, $CDCl_3$) 9.42 (1H, d, *J* 1.3, C*H*O), 7.29–7.12 (5H, m, Ar*H*), 6.45 (1H, ddd, *J* 8.1, 6.8, 1.3, CH_A=CH_B), 6.12 (1H, ddd, *J* 8.1, 6.5, 1.2, CH_A=CH_B), 3.13 (1H, app dt, *J* 6.3, 2.2, C*H*Ph), 3.03–2.98 (1H, m, C*H*CHCHO), 2.76 (1H, app dt, *J* 6.3, 1.5, C*H*CHO), 2.58–2.54 (1H, m, C*H*CHPh), 1.72–1.58 (2H, m, CH_AH$_B$CHCHCHO and CH_AH$_B$CHCHPh), 1.44–1.32 (1H, m, CH$_A$$H_B$CHCHCHO) and 1.07–0.94 (1H, m, CH$_A$$H_B$CHCHPh).

(*S*)-2-((*R*)-2'-Hydroxy-2'-phenylacetyl)-5-phenylpyrazolidin-3-one (5*S*)-127 and (*R*)-2-((*R*)-2'-hydroxy-2'-phenylacetyl)-5-phenylpyrazolidin-3-one (5*R*)-127



(5*S*)-127 **(5*R*)-127**

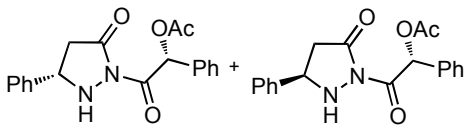
N-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (250 mg, 1.54 mmol), 1-hydroxybenzotriazole (208 mg, 1.54 mmol), (*R*)-mandelic acid (234 mg, 154 mmol) and (*RS*)-5-phenylpyrazolidin-3-one **83** (250 mg, 1.54 mmol) were combined in THF according to general procedure E. The crude material was purified by column chromatography, eluting with 25 % ethyl acetate in petrol then 50 % ethyl acetate in petrol to give title compound **(5*S*)-127** as a white solid (59 mg, 13 %) and title compound **(5*R*)-127** as a clear yellow oil

(67 mg, 15 %). 24 mg of mixed fractions were also collected (150 mg of compounds **(5*S*)-** and **(5*R*)-127** over all fractions, 33 % combined yield).

Compound (5*S*)-127 (upper spot): $[\alpha]^{20}_{D}$ –77.0 (*c* 0.2, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3422 (O-H), 3228 (N-H), 3038 (Ar-H), 3025 (Ar-H), 2947 (C-H), 1751 (C=O) and 1686 (C=O); ***mp*** 143–145 ºC; δ_N ($CDCl_3$) 189 (*N*(2)C(O)), 105 (*N*(1)H); δ_H (300 MHz, $CDCl_3$) 7.47–7.32 (10H, m, Ar*H*), 6.00 (1H, s, C*H*(OH)), 5.17 (1H, bs, O*H*), 4.68 (1H, app dt, *J* 10.1, 7.7, C(5)*H*), 4.06 (1H, d, *J* 7.4, N(2)*H*), 3.01 (1H, dd, ABX system, J_{AB} 17.2, J_{AX} 10.1, C(4)H_AH$_B$) and 2.90 (1H, dd, ABX system, J_{BA} 17.2, J_{BX} 7.7, C(4)H$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 170.8 (*C*(O)), 170.3 (*C*(O)), 138.3 (*C*Ar$_{ipso}$), 137.0 (*C*Ar$_{ipso}$), 129.2 (*C*Ar), 129.0 (*C*Ar), 128.9 (*C*Ar), 128.8 (*C*Ar), 127.8 (*C*Ar), 126.6 (*C*Ar), 73.4 (*C*H(OH)), 58.0 (*C*(5)H) and 41.0 (*C*(4)H_2); ***m/z*** HRMS (ESI^+) $C_{17}H_{17}N_2O_3$ ($[M+H]^+$) requires 297.1234, found 297.1237 (+1.1 ppm).

Compound (5*R*)-127 (lower spot): $[\alpha]^{20}$ –47.3º (*c* 0.1, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3424 (O-H), 3226 (N-H), 3058 (Ar-H), 3025 (Ar-H), 1752 (C=O) and 1700 (C=O); ***mp*** 125–126 ºC; δ_H (300 MHz, $CDCl_3$) 7.39–7.24 (8H, m, Ar*H*), 7.22–7.16 (2H, m, Ar*H*), 5.96 (1H, s, C*H*(OH)), 5.41 (1H, bs, O*H*), 4.62 (1H, app t, *J* 8.0, C(5)*H*), 3.92 (1H, bs, N(2)*H*), 2.99 (1H, dd, ABX system, J_{AB} 17.2, J_{AX} 7.4, C(4)H_AH$_B$) and 2.77 (1H, dd, ABX system, J_{BA} 17.2, J_{BX} 8.9, C(4)H$_A$$H_B$); δ_C (75 MHz, $CDCl_3$) 170.6 (*C*(O)), 170.0 (*C*(O)), 138.1 (*C*Ar$_{ipso}$), 137.7 (*C*Ar$_{ipso}$), 129.1 (*C*Ar), 128.8 (*C*Ar), 127.8 (*C*Ar), 126.5 (*C*Ar), 73.4 (*C*H(OH)), 58.2 (*C*(5)H) and. 41.2 (*C*(4)H_2); ***m/z*** HRMS (ESI^+) $C_{17}H_{17}N_2O_3$ ($[M+H]^+$) requires 297.1234, found 297.1237 (+1.1 ppm).

(*S*)-2-((*R*)-2'-Acetoxy-2'-phenylacetyl)-5-phenylpyrazolidin-3-one (5*S*)-133 and (*R*)-2-((*R*)-2'-Acetoxy-2'-phenylacetyl)-5-phenylpyrazolidin-3-one (5*R*)-133



(5*S*)-133 **(5*R*)-133**

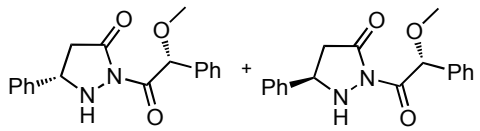
N-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (590 mg, 3.08 mmol), 1-hydroxybenzotriazole (416 mg, 3.08 mmol), (*R*)-acetylmandelic acid (598 mg, 3.08 mmol) and (*RS*)-5-phenylpyrazolidin-3-one **83** (250 mg, 1.54 mmol) were combined according to general procedure E. The crude material was purified by column chromatography, eluting with 25 % ethyl acetate in petrol. Chromatography was then repeated, eluting with 20 % ethyl acetate in petrol to give title compound **(5*S*)-133** as a cream solid (52 mg, 11 %) and title

compound **(5*R*)-133** as a yellow amorphous solid (135 mg, 26 %). 64 mg of mixed fractions were also collected (251 mg of compounds **(5*S*)-** and **(5*R*)-133** over all fractions, 48 % combined yield).

Compound (5*S*)-133 (upper spot): $[\alpha]^{20}_D$ –76.1 (*c* 0.2, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3237 (N-H), 3025 (Ar-H), 2957 (C-H), 1759 (C=O), 1736 (C=O) and 1686 (C=O); ***mp*** 181–183 ºC; δ_H (400 MHz, $CDCl_3$) 7.60–7.56 (2H, Ar*H*), 7.42–7.34 (8H, m, Ar*H*), 6.92 (1H, s, C*H*OC(O)), 4.65 (1H, app q, *J* 8.6, C(5)*H*), 3.42 (1H, d, *J* 5.1 N(2)*H*), 3.00 (1H, d, *J* 7.9, C(4)H_AH_B), 2.91 (1H, d, *J* 9.7, C(4) H_AH_B) and 2.17 (3H, s, C(O)CH_3); δ_C (75 MHz, $CDCl_3$) 170.8 (*C*(O)), 170.6 (*C*(O)), 165.3 (*C*(O)CH_3), 137.4 (*C*Ar_{ipso}) 133.0 (*C*Ar_{ipso}), 129.7 (*C*Ar), 129.25 (*C*Ar), 129.22 (*C*Ar), 129.0 (*C*Ar), 128.9 (*C*Ar), 126.7 (*C*Ar), 74.5 (*C*HOC(O)), 57.8 (*C*(5)H), 41.4 (*C*(4)H_2) and 20.8 (C(O)*C*H_3); ***m/z*** HRMS (ESI^+) $C_{19}H_{19}N_2O_4$ ($[M+H]^+$) requires 339.1339, found 339.1342 (+0.8 ppm).

Compound (5*R*)-133 (lower spot): $[\alpha]^{20}_D$ –37.6 (*c* 0.4, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3259 (N-H), 3064 (Ar-H), 3034 (Ar-H), 1747 (C=O), 1714 (C=O) and 1695 (C=O); ***mp*** 49–51 ºC; δ_H (400 MHz, $CDCl_3$) 7.58–7.54 (2H, m, Ar*H*), 7.41–7.36 (4H, m, Ar*H*), 7.33–7.26 (4H, m, Ar*H*), 6.92 (1H, s, C*H*OC(O)), 5.63 (1H, bs, N(2)*H*), 4.74 (1H, app t, *J* 7.9, C(5)*H*), 3.07 (1H, dd, ABX system, J_{AB} 17.1, J_{AX} 7.3, C(4)H_AH_B), 2.82 (1H, dd, ABX system, J_{BA} 17.1, J_{BX} 9.9, C(4)H_AH_B) and 2.18 (3H, s, C(O)CH_3); δ_C (100 MHz, $CDCl_3$) 170.9 (*C*(O)), 170.8 (*C*(O)), 165.0 (*C*(O)CH_3), 137.8 (*C*Ar_{ipso}), 132.8 (*C*Ar_{ipso}), 129.7 (*C*Ar), 129.2 (*C*Ar), 129.0 (*C*Ar), 128.9 (*C*Ar), 128.7 (*C*Ar), 126.6 (*C*Ar), 74.4 (*C*HOC(O)), 58.2 (*C*(5)H), 41.7 (*C*(4)H_2) and 20.8 (C(O)*C*H3); ***m/z*** HRMS (ESI^+) $C_{19}H_{18}N_2O_4Na$ ($[M+Na]^+$) requires 361.1159, found 361.1161 (+2.6 ppm).

(*S*)-2-((*R*)-2'-Methoxy-2'-phenylacetyl)-5-phenylpyrazolidin-3-one (5*S*)-134 and (*R*)-2-((*R*)-2'-methoxy-2'-phenylacetyl)-5-phenylpyrazolidin-3-one (5*R*)-134



(5*S*)-134 **(5*R*)-134**

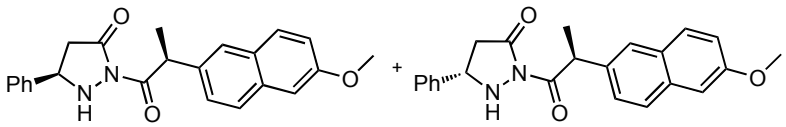
N-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (14.4 g, 75.3 mmol), 1-hydroxybenzotriazole (10.2 g, 75.3 mmol), (*R*)-α-methylmandelic acid (12.5 g, 75.3 mmol) and (*RS*)-5-phenylpyrazolidin-3-one **83** (12.2 g, 75.3 mmol) were combined according to general procedure E. The crude material was purified by column chromatography, eluting with

35 % ethyl acetate in petrol to give first the title compound **(5*S*)-134** as an amorphous yellow solid (1.17 g, 5 %) and then title compound **(5*R*)-134** as a cream solid (1.60 g, 7 %). 10.9 g of mixed fractions were also collected and subjected again to column chromatography, eluting with 25 % ethyl acetate in petrol to give more compound **(5*S*)-134** (830 mg, 4 %), compound **(5*R*)-134** (3.76 g, 16 %) and 5.01 g of mixed fractions (12.4 g of compounds **(5*S*)-** and **(5*R*)-134** over all fractions, 53 % combined yield).

Compound (5*S*)-134 (upper spot): $[\alpha]^{20}_D$ −62.6 (*c* 0.5, dichloromethane); ν_{max} (KBr disc)/ cm^{-1} 3246 (N-H), 3064 (Ar-H), 3025 (Ar-H), 2927 (C-H), 1750 (C=O) and 1701 (C=O); ***mp*** 43–46 ºC; δ_N ($CDCl_3$) 192 (*N*(2)C(O)), 104 (*N*(1)H); δ_H (300 MHz, $CDCl_3$) 7.55–7.53 (2H, m, Ar*H*), 7.41–7.33 (8H, m, Ar*H*), 5.87 (1H, s, C*H*OCH_3), 4.61 (1H, app dt, *J* 10.0, 7.4, C(5)*H*), 3.40 (3H, s, OCH_3), 3.00 (1H, dd, ABX system, J_{AB} 17.1, J_{AX} 7.6, C(4)$H_A$$H_B$) and 2.93 (1H, dd, ABX system, J_{BA} 17.1, J_{BX} 10.0, C(4)$H_A$$H_B$); δ_C (75 MHz, $CDCl_3$) 170.0 (N(2)*C*(O)), 167.2 (N(1)*C*(O)), 137.5 (*C*Ar_{ipso}), 135.7 (*C*Ar_{ipso}), 129.2 (*C*Ar), 128.9 (*C*Ar), 128.8 (*C*Ar), 126.7 (*C*Ar), 81.7 (*C*HOCH3), 57.7 (*C*(5)H), 57.4 (CHO*C*H_3) and 41.7 (*C*(4)H_2); ***m/z*** HRMS (ESI^+) $C_{18}H_{19}N_2O_3$ ($[M+H]^+$) requires 311.1390, found 311.1396 (+1.9 ppm).

Compound (5*R*)-134 (lower spot): $[\alpha]^{20}_D$ −1.5 (*c* 1.0, dichloromethane); ν_{max} (KBr disc)/ cm^{-1} 3231 (N-H), 3025 (Ar-H), 2985 (C-H), 2934 (C-H), 1744 (C=O) and 1701 (C=O); ***mp*** 140–144 ºC; δ_N ($CDCl_3$) 190 (*N*(2)C(O)), 104 (*N*(1)H); δ_H (400 MHz, $CDCl_3$) 7.52 (2H, dd, *J* 6.6, 3.2, Ar*H*), 7.38–7.34 (3H, m, Ar*H*), 7.31–7.27 (3H, m, Ar*H*), 7.23–7.21 (2H, m, Ar*H*), 5.89 (1H, s, C*H*OCH_3), 4.71 (1H, dd, *J* 9.3, 7.5, C(5)*H*), 3.40 (3H, s, OCH_3), 3.07 (1H, dd, ABX system, J_{AB} 17.1, J_{AX} 7.5, C(4)$H_A$$H_B$) and 2.82 (1H, dd, ABX system, J_{BA} 17.1, J_{BX} 9.3, C(4)$H_A$$H_B$); δ_C (75 MHz, $CDCl_3$) 169.9 (N(2)*C*(O)), 167.0 (N(1)*C*(O)), 138.0 (*C*Ar_{ipso}), 135.4 (*C*Ar_{ipso}), 129.2 (*C*Ar), 129.1 (*C*Ar), 128.8 (*C*Ar), 128.7 (*C*Ar), 126.5 (*C*Ar), 81.6 (*C*HOCH3), 58.1 (*C*(5)H), 57.4 (CHO*C*H_3) and 41.9 (*C*(4)H_2); ***m/z*** HRMS (ESI^+) $C_{18}H_{19}N_2O_3$ ($[M+H]^+$) requires 311.1390, found 311.1393 (+0.9 ppm).

(*R*)-2-((*S*)-2'-(6-Methoxynaphthalen-2-yl)propanoyl)-5-phenylpyrazolidin-3-one (5*R*)-135 and (*S*)-2-((*S*)-2'-(6-methoxynaphthalen-2-yl)propanoyl)-5-phenylpyrazolidin-3-one (5*S*)-135



(5*R*)-135 **(5*S*)-135**

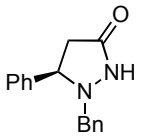
N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (26.5 g. 138 mmol), 1-hydroxybenzotriazole (18.7 g, 138 mmol), (*S*)-Naproxen (31.9 g, 138 mmol) and (*RS*)-5-phenylpyrazolidin-3-one **83** (22.5 g, 138 mmol) were combined according to general procedure E. The crude material was purified by Biotage Isolera on silica gel, eluting with a gradient of 10-90 % ethyl acetate in heptane to give title compound **(5*R*)-135** as a colourless solid (7.20 g, 14 %) and 20.9 g of mixed fractions (28.1 g of compounds **(5*R*)-** and **(5*S*)-135** over all fractions, 54 % combined yield). In order to access pure compound **(5*S*)-135**, 2.02 g of mixed fractions were further purified by column chromatography on silica gel, eluting with 1-2 % ethyl acetate in dichloromethane to give 480 mg of fractions enriched in **(5*S*)-135** and 1.50 g mixed fractions. These enriched fractions were further purified by column chromatography on silica gel, eluting with 1-2 % ethyl acetate in dichloromethane to give pure compound **(5*S*)-135** as a colourless oil (60.0 mg, 0.1 %).

Compound (5*R*)-135 (upper spot): $[\alpha]^{20}_D$ +64.8 (*c* 1.0, dichloromethane); ν_{max} (KBr disc)/ cm^{-1} 3255 (N-H) 3050 (Ar-H), 2966 (C-H), 2956 (C-H), 1744 (C=O), 1686 (C=O), 1630 (N-H bend) and 1603 (Ar C=C); ***mp*** 157–160 ˚C; δ_N ($CDCl_3$) 193 (*N*(2)C(O)), 104 (*N*(1)H); δ_H (300 MHz, $CDCl_3$) 7.74–7.68 (3H, m, Ar*H*), 7.48 (1H, dd, *J* 8.5, 1.8, Ar*H*), 7.38–7.32 (5H, m, Ar*H*), 7.10–7.05 (2H, m, Ar*H*), 5.04 (1H, q, *J* 6.9, C*H*(CH_3)), 4.58 (1H, dd, *J* 10.0, 8.2, C(5)*H*), 3.91 (3H, s, OCH_3), 2.95 (1H, d, *J* 8.2, C(4)H_AH$_B$), 2.93 (1H, d, *J* 10.0, C(4)H$_A$$H_B$) and 1.56 (3H, d, *J* 7.0, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 171.0 (N(2)*C*(O)), 169.7 (*C*(3)O), 157.8 (O*C*Ar$_{ipso}$), 137.8 (*C*Ar$_{ipso}$), 135.8 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.5 (*C*Ar), 129.0 (*C*Ar), 128.7 (*C*Ar), 127.2 (*C*Ar), 127.0 (*C*Ar), 126.7 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 57.2 (*C*(5)H), 55.0 (O*C*H$_3$), 44.2 (*C*H(CH_3)), 42.0 (*C*(4)H$_2$) and 19.4 (CH(*C*H$_3$)); ***m/z*** HRMS (ESI^+) $C_{23}H_{23}N_2O_3$ ($[M+H]^+$) requires 375.1703, found 375.1702 (–0.3 ppm).

Compound (5*S*)-135 (lower spot): $[\alpha]^{20}_D$ +20.8 (*c* 0.25, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3266 (N-H) 3059 (Ar-H), 2916 (C-H), 2842 (C-H), 1744 (C=O), 1692 (C=O), 1631 (N-H bend) and 1604 (Ar C=C); ***mp*** 47–51 ˚C; δ_H (300 MHz, $CDCl_3$) 7.72–7.68 (3H, m, Ar*H*), 7.47 (1H, dd, *J* 8.5, 1.7, Ar*H*), 7.28–7.21 (5H, m, Ar*H*), 7.15–7.11 (2H, m, Ar*H*), 5.60 (1H, d, *J* 6.8, N(1)*H*), 5.07 (1H, q, *J* 7.0, C*H*(CH_3)), 4.66 (1H, app dt, *J* 9.3, 7.1, C(5)*H*), 3.92 (3H, s, OCH_3), 3.05 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 7.3, C(4)H_AH$_B$), 2.80 (1H, dd, J_{BA} 17.0, J_{BX} 9.3,

C(4)H$_A$*H$_B$*) and 1.58 (3H, d, *J* 7.0, CH(C*H$_3$*)); ***δ$_C$*** (75 MHz, $CDCl_3$) 170.8 (N(2)*C*(O)), 169.6 (*C*(3)O), 157.8 (O*C*Ar$_{ipso}$), 138.3 (*C*Ar$_{ipso}$), 135.6 (*C*Ar$_{ipso}$), 133.9 (*C*Ar$_{ipso}$), 129.5 (*C*Ar), 129.1 (*C*Ar$_{ipso}$), 129.0 (*C*Ar), 128.6 (*C*Ar), 127.3 (*C*Ar), 127.1 (*C*Ar), 126.6 (*C*Ar), 126.5 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 57.6 (*C*(5)H), 55.5 (O*C*H$_3$), 44.2 (*C*H(CH$_3$)), 42.1 (*C*(4)H$_2$) and 19.4 (CH(*C*H$_3$)); ***m/z*** HRMS (ESI$^+$) $C_{23}H_{22}N_2O_3Na$ ([M+Na]$^+$) requires 397.1528, found 375.1529 (+0.2 ppm).

(*R*)-1-Benzyl-5-phenylpyrazolidin-3-one (*R*)-138



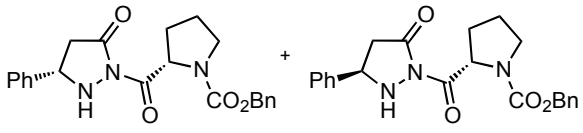
(*R*)-138

To a solution of (*R*)-5-phenylpyrazolidin-3-one **(*R*)-83** (42 mg, 0.259 mmol) in ethanol (1 mL) was added benzaldehyde (0.1 mL, 1.03 mmol) and the resulting mixture left to stir at room temperature overnight. Sodium borohydride (49 mg, 1.30 mmol) was then added and the mixture stirred for a further hour. The reaction mixture was partitioned between water (5 mL), saturated sodium hydrogen carbonate solution (5 mL) and dichloromethane (10 mL). The resulting aqueous layer was extracted with further dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography, eluting with 40 % ethyl acetate in petrol to give the title compound as a colourless solid with an enantiomeric excess of 95 % and spectroscopic data in accordance with the literature (33 mg, 51 %).[95,147]

[α]$^{20}_D$ +168 (*c* 0.9, dichloromethane), lit. $[\alpha]^{20}_D$ −163 ((*S*)-enantiomer, *c* 0.90, dichloromethane);[34] ***mp*** 106–109 ºC; ***δ$_H$*** (400 MHz, $CDC1_3$) 7.48 (1H, bs, N(2)*H*), 7.40–7.37 (2H, m, Ar*H*), 7.35–7.20 (8H, m, Ar*H*), 4.15 (1H, app t, *J* 8.6, C(5)*H*), 3.95 (1H, d, AB system, J_{AB} 12.9, C*H$_A$*H$_B$*Ph), 3.56 (1H, d, AB system, J_{BA} 12.9, CH$_A$*H$_B$*Ph), 2.90 (1H, dd, ABX system, J_{AB} 16.8, J_{AX} 8.3, C(4)*H$_A$*H$_B$*) and 2.47 (1H, dd, ABX system, J_{BA} 16.8, J_{BX} 8.9, C(4)H$_A$*H$_B$*).

Enantiomeric excess was determined by HPLC with Chiralpak AD-H (7 % isopropanol/hexane, flow rate = 1.0 mL/min, 220 nm), t_R(*S*) 17.3 min and t_R(*R*) 20.5 min. Absolute configuration determined by comparison of the optical rotation to literature value.[95]

(*S*)-2-((*S*)-1'-((benzyloxy)carbonyl)pyrrolidine-2'-carbonyl)-5-phenylpyrazolidin-3-one (5*S*)-142 and (*R*)-2-((*S*)-1'-((benzyloxy)carbonyl)pyrrolidine-2'-carbonyl)-5-phenylpyrazolidin-3-one (5*R*)-142



(5*S*)-142 **(5*R*)-142**

Benzyl chloroformate (9.5 mL, 65 mmol) and 4 M sodium hydroxide solution (18.0 mL, 70 mmol) were added dropwise simultaneously (using addition funnels) over 30 min with vigorous stirring to an ice-cooled solution of (*S*)-proline **14** (5.80 g, 50 mmol) in 2 M sodium hydroxide solution (30.0 mL, 60 mmol). The reaction was then left to stir at room temperature for 1 h. The solution was then extracted with diethyl ether (2 × 50 mL) and the aqueous layer retained and acidified to approximately pH 4 with 2 M HCl. The resulting solution was extracted with ethyl acetate (3 × 50 mL), the organic layers dried ($MgSO_4$) and concentrated *in vacuo* to give crude (*S*)-*N*-(benzyloxycarbonyl)-proline **141** (10.1 g) as a colourless oil with spectroscopic data in accordance with the literature.[148] Product was used without further purification.

$\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$, rotamers A:B 1.4:1) 7.39–7.27 (A, 5H, m, Ar*H* & B, 5H, m, Ar*H*), 5.18 (A, 1H, d, AB system, J_{AB} 12.4, PhCH_AH$_B$), 5.15 (A, 1H, d, AB system, J_{AB} 12.4, PhCH$_A$$H_B$), 5.13 (B, 2H, s, PhC$H_2$), 4.42 (A, 1H, dd, *J* 8.2, 3.4, N_{Pro}C*H*), 4.38 (B, 1H, dd, *J* 8.7, 3.5, N_{Pro}C*H*), 3.67–3.42 (A, 2H, m, N_{Pro}CH_2 & B, 2H, m, N_{Pro}CH_2) and 2.35–1.86 (A, 4H, m, CH_2CH_2 & B, 4H, m, CH_2CH_2).

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.09 g, 5.67 mmol), 1-hydroxybenzotriazole (766 mg, 5.67 mmol), (*S*)-*N*-(benzyloxycarbonyl)-proline **141** (1.55 g, 6.24 mmol, added as solution in 5 mL DMF) and (*RS*)-5-phenylpyrazolidin-3-one **83** (1.00 g, 5.67 mmol) were combined according to general procedure E. The crude material was purified by column chromatography, eluting with 40 % ethyl acetate in petrol to give title compound **(5*S*)-142** as a clear yellow oil (382 mg, 17 %) and fractions containing title compound **(5*R*)-142** and a minor impurity (176 mg). 392 mg of mixed fractions were also collected. The fractions containing impure **(5*R*)-142** were purified by further column chromatography, eluting with diethyl ether to give title compound **(5*R*)-142** as a colourless oil (100 mg, 4 %) (668 mg of compounds **(5*S*)-** and **(5*R*)-142** over all fractions, 30 % combined yield).

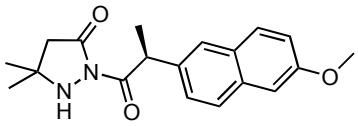
Compound (5*S*)-142 (upper spot): $\boldsymbol{[\alpha]^{20}_D}$ –82.2 (*c* 0.6, chloroform); $\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3248 (N-H), 3063 (Ar-H), 3033 (Ar-H), 2978 (C-H), 2955 (C-H), 2883 (C-H), 1771 (C=O),

1746 (C=O), 1695 (C=O), 1605 (N-H bend) and 1586 (Ar C=C); $\boldsymbol{\delta_N}$ ($CDCl_3$) 192 (*N*(2)C(O)), 103 (*N*(1)H), 97.8 (N_{Pro}C(O)O); $\boldsymbol{\delta_H}$ (500 MHz, $(CD_3)_2S(O)$, rotamers A:B 1.1:1) 7.46 (A, 2H, d, *J* 7.3, Ar*H*), 7.39–7.36 (A, 4H, m, Ar*H* & B, 4H, m, Ar*H*), 7.33–7.27 (A, 4H, m, Ar*H* & B, 4H, m, Ar*H*), 7.24 (B, 2H, d, *J* 6.8, Ar*H*), 6.54 (B, 1H, d, *J* 9.0, N(1)*H*), 6.53 (A, 1H, d, *J* 8.9, N(1)*H*), 5.22–5.14 (A, 1H, m, $N_{Pro}CH$ & B, 1H, m, $N_{Pro}CH$), 5.08 (A, 2H, s, PhCH_2), 5.03 (B, 1H, d, AB system, J_{AB} 13.1, PhCH_AH$_B$), 4.97 (B, 1H, d, AB system, J_{BA} 13.1, PhCH$_A H_B$), 4.67 (A, 1H, app q, *J* 8.3, C(5)*H*), 4.58 (B, 1H, br s, C(5)*H*), 3.53–3.38 (A, 2H, m, $N_{Pro}CH_2$ & B, 2H, m, $N_{Pro}CH_2$), 3.10 (B, 1H, dd, ABX system, J_{AB} 16.9, J_{AX} 9.0, C(4)H_AH$_B$), 3.08 (A, 1H, dd, ABX system, J_{AB} 16.7, J_{AX} 7.1, C(4)H_AH$_B$), 2.92 (A, 1H, dd, ABX system, J_{BA} 16.7, J_{BX} 9.6, C(4)H$_A H_B$), 2.81 (B, 1H, dd, ABX system, J_{BA} 16.7, J_{BX} 8.7, C(4)H$_A H_B$), 2.31–2.19 (A, 1H, m, N_{Pro}CHCH_AH$_B$ & B, 1H, m, N_{Pro}CHCH_AH$_B$) and 1.95–1.84 (A, 3H, m, N_{Pro}CHCH$_A H_B CH_2$ & B, 3H, m, N_{Pro}CHCH$_A H_B CH_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.8 (*C*(3)O), 169.7 (*C*(3)O), 169.1 (N(2)*C*(O)), 168.5 (N(2)*C*(O)), 155.0 (*C*(O)O), 154.1 (*C*(O)O), 137.9 (*C*Ar$_{ipso}$), 137.7 (*C*Ar$_{ipso}$), 136.9 (*C*Ar$_{ipso}$), 136.8 (*C*Ar$_{ipso}$), 129.1 (*C*Ar), 128.79 (*C*Ar), 128.77 (*C*Ar), 128.6 (*C*Ar), 128.5 (*C*Ar), 128.3 (*C*Ar), 128.2 (*C*Ar), 128.1 (*C*Ar), 127.9 (*C*Ar), 126.9 (*C*Ar), 126.7 (*C*Ar), 67.2 (*C*H$_2$Ph), 67.1 (*C*H$_2$Ph), 59.8 (N_{Pro}*C*H), 58.7 (N_{Pro}*C*H), 58.2 (*C*(5)H), 58.0 (*C*(5)H), 47.4 (N_{Pro}*C*H$_2$), 47.0 (N_{Pro}*C*H$_2$), 42.0 (*C*(4)H$_2$), 41.9 (*C*(4)H$_2$), 30.7 (N_{Pro}CH*C*H$_2$CH$_2$), 29.8 (N_{Pro}CH*C*H$_2$CH$_2$), 24.1 (N_{Pro}CHCH$_2$*C*H$_2$) and 23.6 (N_{Pro}CHCH$_2$*C*H$_2$); ***m/z*** HRMS (ESI^+) $C_{22}H_{24}N_3O_4$ ([M+H]$^+$) requires 394.1761, found 394.1765 (+0.9 ppm).

Compound (5*R*)-142 (lower spot): $\boldsymbol{[\alpha]^{20}_D}$ –40.3 (*c* 0.9, chloroform); $\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3226 (N-H), 3059 (Ar-H), 3029 (Ar-H), 2956 (C-H), 2926 (C-H), 1744 (C=O), 1708 (C=O), 1695 (C=O) and 1605 (N-H bend); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$, rotamers A:B 1.1:1) 7.56–7.19 (A, 10H, m, Ar*H* & B, 10H, m, Ar*H*), 5.40 (A, 1H, d, *J* 8.7, $N_{Pro}CH$), 5.39 (B, 1H, d, *J* 8.5, $N_{Pro}CH$), 5.17 (A, 1H, d, AB system, J_{AB} 12.5, PhCH_AH$_B$), 5.10 (A, 1H, d, AB system, J_{BA} 12.5, PhCH$_A H_B$), 5.09 (B, 1H, d, AB system, J_{AB} 12.3, PhCH_AH$_B$), 5.03 (B, 1H, d, AB system, J_{BA} 12.3, PhCH$_A H_B$), 4.75 (A, 1H, app t, *J* 8.8, C(5)*H*), 4.64 (B, 1H, app t, *J* 8.6, C(5)*H*), 3.74–3.49 (A, 2H, m, $N_{Pro}CH_2$ & B, 2H, m, $N_{Pro}CH_2$), 3.039 (A, 1H, d, *J* 8.6, C(4)H_AH$_B$), 3.038 (A, 1H, d, *J* 9.4, C(4)H$_A H_B$), 2.97 (B, 1H, dd, ABX system, J_{AB} 17.0, J_{AX} 7.3, C(4)H_AH$_B$), 2.74 (B, 1H, dd, ABX system, J_{BA} 17.0, J_{BX} 10.5, C(4)H$_A H_B$), 2.44–2.30 (A, 1H, m, N_{Pro}CHCH_AH$_B$ & B, 1H, m, N_{Pro}CHCH_AH$_B$) and 2.08–1.89 (A, 3H, m, N_{Pro}CHCH$_A H_B CH_2$ & B, 3H, m, N_{Pro}CHCH$_A H_B CH_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 170.9 (*C*(3)O), 170.7 (*C*(3)O), 169.6 (N(2)*C*(O)), 169.1 (N(2)*C*(O)), 155.0 (*C*(O)O), 154.2 (*C*(O)O), 137.6 (*C*Ar$_{ipso}$), 137.5 (*C*Ar$_{ipso}$), 136.9 (*C*Ar$_{ipso}$), 129.2 (*C*Ar), 129.1 (*C*Ar), 129.0 (*C*Ar), 128.9 (*C*Ar),

128.6 (2 x *C*Ar), 128.05 (*C*Ar), 128.03 (*C*Ar), 128.0 (*C*Ar), 127.9 (*C*Ar), 126.8 (*C*Ar), 126.6 (*C*Ar), 67.2 (2 x *C*H_2Ph), 60.1 (N_{Pro}*C*H), 59.2 (N_{Pro}*C*H), 57.8 (*C*(5)H), 57.4 (*C*(5)H), 47.4 (N_{Pro}*C*H_2), 46.9 (N_{Pro}*C*H_2), 41.5 (*C*(4)H_2), 41.3 (*C*(4)H_2), 31.0 (N_{Pro}CH*C*H_2CH_2), 30.1 (N_{Pro}CH*C*H_2CH_2), 24.1 (N_{Pro}CHCH_2*C*H_2) and 23.5 (N_{Pro}CHCH_2*C*H_2); ***m/z*** HRMS (ESI^+) $C_{22}H_{24}N_3O_4$ ($[M+H]^+$) requires 394.1761, found 394.1755 (–1.6 ppm).

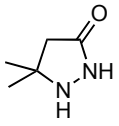
(S)-2-(2'-(6-Methoxynaphthalen-2-yl)propanoyl)-5,5-dimethylpyrazolidin-3-one 143



143

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.11 g, 5.80 mmol), 1-hydroxybenzotriazole (784 mg, 5.80 mmol), (*S*)-Naproxen (1.34 g, 5.80 mmol) and 5,5-dimethylpyrazolidin-3-one **145** (662 mg, 5.80 mmol) were combined according to general procedure E. The crude material was purified by column chromatography on silica gel, eluting with 75 % diethyl ether in petrol to give the title compound as a colourless solid (1.15 g, 61 %). $[\alpha]^{20}_D$ +20.8 (*c* 0.25, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3226 (N-H) 2967 (C-H), 2927 (C-H), 1764 (C=O), 1747 (C=O), 1673 (N-H bend), 1633 (Ar C=C) and 1609 (Ar C=C); ***mp*** 109–111 ˚C; δ_N ($CDCl_3$) 190 (*N*(2)C(O)), 117 (*N*(1)H); δ_H (400 MHz, $CDCl_3$) 7.71–7.66 (3H, m, Ar*H*), 7.44 (1H, dd, *J* 8.6, 1.7, Ar*H*), 7.14–7.08 (2H, m, Ar*H*), 4.99 (1H, q, *J* 6.9, C*H*(CH_3)), 3.90 (3H, s, OCH_3), 2.53 (1H, d, AB system, J_{AB} 16.8, C(4)$H_A$$H_B$), 2.45 (1H, d, AB system, J_{BA} 16.8, C(4)$H_A$$H_B$), 1.55 (3H, d, *J* 7.0, ArCH(CH_3)), 1.28 (3H, s, (C((CH_3)$_A$(CH_3)$_B$)) and 1.14 (3H, s, (C((CH_3)$_A$(CH_3)$_B$)); δ_C (100 MHz, $CDCl_3$) 171.8 (*C*(O)), 171.7 (*C*(O)), 157.7 (O*C*Ar$_{ipso}$), 135.9 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.5 (*C*Ar), 129.1 (*C*Ar$_{ipso}$), 127.2 (*C*Ar), 127.0 (*C*Ar), 126.5 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 55.5 (*C*(CH_3)$_2$), 55.4 (O*C*H_3), 47.9 (*C*(4)H_2), 44.5 (*C*H(CH_3)), 26.2 (C((*C*H_3)$_A$(CH_3)$_B$)), 26.1 (C((CH_3)$_A$(*C*H_3)$_B$)) and 19.4 (CH(*C*H_3)); ***m/z*** HRMS (ESI^+) $C_{19}H_{22}N_2O_3Na$ ($[M+Na]^+$) requires 349.1528, found 349.1534 (+0.6 ppm).

5,5-Dimethylpyrazolidin-3-one 147

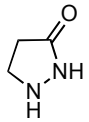


147

To a solution of hydrazine hydrate (2.35 mL, 48.2 mmol) in absolute ethanol (50 mL) was added methyl 3-methyl-2-butenoate **145** (5.30 mL, 43.8 mmol) by dropwise addition. The resulting solution was stirred for 1 h at rt and then at reflux for 4 h before concentration *in vacuo* to give the title compound as a colourless oil with spectroscopic data in accordance with the literature (4.95 g, 99 %).[75]

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.28 (1H, br s, N(2)*H*), 4.08 (1H, br s, N(1)*H*), 2.31 (2H, s, C(4)H_2) and 1.29 (6H, s, C(CH_3)$_2$).

Pyrazolidin-3-one 148

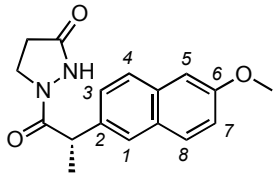


148

To a solution of hydrazine hydrate (6.20 mL, 0.130 mol) in absolute ethanol (100 mL) was added methyl acrylate **146** (10.4 mL, 0.120 mol) by dropwise addition causing significant heat evolution. The resulting solution was stirred for 1 h at rt and then at reflux for 4 h before concentration *in vacuo*. The resultant material was taken up in toluene (100 mL) and subjected to reflux overnight. The crude material was then purified by column chromatography on silica gel, eluting with 10 % methanol in dichloromethane to give the title compound as a viscous oil with spectroscopic data in accordance with the literature (1.05 g, 10 %).[75]

$\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 5.26 (2H, bs, N(1)*H* & N(2)*H*), 3.50 (2H, t, *J* 7.7, C(5)H_2) and 2.49 (2H, t, *J* 7.7, C(4)H_2).

(*S*)-1-(2'-(6-Methoxynaphthalen-2-yl)propanoyl)pyrazolidin-3-one 149



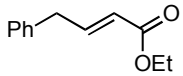
149

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.11 g, 5.80 mmol), 1-hydroxybenzotriazole (784 mg, 5.80 mmol), (*S*)-Naproxen (1.34 g, 5.80 mmol) and pyrazolidin-3-one **148** (500 mg, 5.80 mmol) were combined according to general procedure E. The crude material was purified by column chromatography on silica gel, eluting with 50 % diethyl ether in petrol then 5 % methanol in dichloromethane. The resultant oil was then triturated in diethyl ether and filtered to give the title compound as a grey solid (381 mg, 22 %). $[\alpha]^{20}_{D}$ +5.8 (*c* 0.52, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3190 (N-H) 2959 (C-H), 2932 (C-H), 1716 (C=O), 1691 (C=O), 1631 (N-H bend) and 1604 (Ar C=C); ***mp*** 167–170 ˚C; δ_N ($CDCl_3$) 142; δ_H (400 MHz, CD_3CN) 9.02 (1H, bs, (N(2)*H*), 7.76–7.71 (3H, m, Ar*H*), 7.43 (1H, d, *J* 8.3, Ar*H*), 7.24 (1H, d, *J* 2.5, Ar*H*), 7.14 (1H, d, *J* 8.9, 2.5, Ar*H*), 4.17 (1H, br s, C(5)H_AH_B), 3.94 (1H, br s, C*H*(CH_3)), 3.89 (3H, s, OCH_3), 3.81 (1H, br s, C(5)H_AH_B), 2.67 (1H, br s, C(4)H_AH_B), 2.54 (1H, ddd, *J* 16.9, 10.2, 6.8, C(5)H_AH_B) and 1.45 (3H, d, *J* 6.9, CH(CH_3)); δ_C (75 MHz, CD_3CN) 170.1 (*C*(3)O), 166.4 (N(1)*C*(O)), 158.7 (O*C*Ar_{ipso}), 137.2 (*C*Ar_{ipso}), 134.7 (*C*Ar_{ipso}), 130.1 (*C*Ar), 129.9 (*C*Ar_{ipso}), 128.2 (*C*Ar), 127.2 (*C*Ar), 126.8 (*C*Ar), 119.8 (*C*Ar), 106.7 (*C*Ar), 56.0 (O*C*H_3), 44.8 (*C*(4)H_2), 42.6 (*C*H(CH_3)), 31.8 (*C*(5)H_2), and 19.8 (CH(*C*H_3)); ***m/z*** HRMS (ESI^+) $C_{17}H_{19}N_2O_3$ ($[M+H]^+$) requires 299.1390, found 299.1391 (+0.3 ppm).

Upon heating to 70 ˚C, the observed rotamers had almost fully coalesced:

δ_H (400 MHz, CD_3CN) 7.75 (2H, app d, *J* 8.7, CAr(4)*H* & CAr(8)*H*), 7.72 (1H, s, CAr(1)*H*), 7.44 (1H, d, *J* 8.5, CAr(3)*H*), 7.24 (1H, d, *J* 2.4, CAr(5)*H*), 7.15 (1H, dd, *J* 8.9, 2.4, CAr(7)*H*), 4.15 (1H, app q, *J* 8.6, C(5)H_AH_B), 3.99 (1H, q, *J* 7.0 C*H*(CH_3)), 3.92–3.87 (1H, m, C(5)H_AH_B), 3.90 (3H, s, OCH_3), 2.65 (1H, m, C(4)H_AH_B), 2.55 (1H, ddd, *J* 16.9, 10.0, 6.9, C(5)H_AH_B), 2.26 (1H, bs, (N(2)*H*) and 1.50 (3H, d, *J* 7.0, CH(CH_3)).

(*E*)-Ethyl 4-phenylbut-2-enoate 152



152

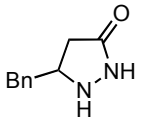
Triethyl phosphite **150** (27.8 mL, 0.16 mol) was added slowly to ethyl bromoacetate (16.6 mL, 0.16 mol) and the resultant solution stirred at reflux for 2 h, then cooled to rt and concentrated *in vacuo* to give ethyl 2-(diethoxyphosphoryl)acetate **151** as a clear oil, with ^{1}H NMR in accordance with the literature (35.6 g, 99 %).[149]

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.14 (4H, q, *J* 7.2, P(O)OCH_2CH$_3$), 4.10 (2H, q, *J* 7.0, C(O)OCH_2CH$_3$), 2.89 (2H, d, *J* 21.6, P(O)CH_2C(O)), 1.28 (6H, t, *J* 7.2, P(O)OCH$_2$CH_3) and 1.22 (3H, t, *J* 7.0, C(O)OCH$_2$CH_3).

Methylmagnesium bromide (3.0 M solution in diethyl ether, 10.4 mL, 31.2 mmol) was added dropwise to a solution of ethyl 2-(diethoxyphosphoryl)acetate **151** (7.00 g, 31.2 mmol) in THF (250 mL) at 0 ºC before being warmed to rt. After 20 min, phenylacetaldehyde (4.0 mL, 34.4 mmol) was added dropwise and the resulting mixture stirred at reflux for 3 h. The reaction was quenched with saturated ammonium chloride solution (120 mL) and the resulting biphasic mixture extracted with diethyl ether (200 mL). It was also necessary to add water (30 mL) in order to achieve efficient separation. The resulting aqueous layer was extracted with more diethyl ether (200 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was then purified by column chromatography, eluting with 5 % diethyl ether in petrol to give the product as a colourless oil, with spectroscopic data in accordance with the literature (3.64 g, 61 %).[101]

$\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.37–7.30 (2H, m, Ar*H*), 7.28–7.16 (3H, m, Ar*H*), 7.12 (1H, dt, *J* 15.6, 6.8, C*H*CHCO$_2$), 5.83 (1H, dt, *J* 15.6, 1.5, C*H*CO$_2$), 4.19 (2H, q, *J* 7.1, OCH_2CH$_3$), 3.54 (2H, dd, J 6.8, 1.5, PhCH_2) and 1.29 (3H, t, *J* 7.1, OCH$_2$CH_3).

(*RS*)-5-benzylpyrazolidin-3-one 153



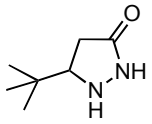
153

To a solution of hydrazine hydrate (9.20 mL, 189 mmol) in absolute ethanol (120 mL) was added (*E*)-ethyl 4-phenylbut-2-enoate **152** (12.0 g, 63.1 mmol) and the resulting solution stirred at reflux for 90 min. The suspension was then concentrated *in vacuo* and redissolved in toluene

(120 mL) and stirred at reflux for a further 90 min. The resulting solution was concentrated *in vacuo* and purified by column chromatography on silica gel, eluting with a gradient of 1-10 % methanol in dichloromethane to give the title compound as an off-white solid (6.96 g, 63 %).

$\boldsymbol{\nu}_{\mathbf{max}}$ (KBr disc)/ cm^{-1} 3234 (N-H), 3165 (N-H), 3054 (Ar-H), 1698 (C=O) and 1655 (N-H bend); ***mp*** 81–83 ˚C; $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.37–7.17 (5H, m, Ar*H*), 3.95 (1H, app quin, *J* 7.2, C(5)*H*), 2.98 (1H, dd, ABX system, J_{AB} 13.8, J_{AX} 6.9, CH_AH$_B$Ph), 2.84 (1H, dd, ABX system, J_{BA} 13.8, J_{BX} 7.0, CH$_A$$H_B$Ph), 2.55 (1H, dd, ABX system, J_{AB} 16.4, J_{AX} 7.2, C(4)H_AH$_B$) and 2.32 (1H, dd, ABX system, J_{BA} 16.4, J_{BX} 7.5, C(4)H$_A$$H_B$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 177.0 (*C*(3)O), 137.3 (*C*Ar$_{ipso}$), 129.2 (*C*Ar), 128.8 (*C*Ar), 127.0 (*C*Ar), 61.0 (*C*(5)H), 39.6 (*C*(4)H_2) and 37.3 (*C*H_2Ph); ***m/z*** HRMS (ESI^+) $C_{10}H_{13}N_2O$ ($[M+H]^+$) requires 177.1022, found 177.1019 (–1.9 ppm).

(*RS*)-5-(*tert*-Butyl)pyrazolidin-3-one 156



156

Butyllithium (2.5 M solution in hexanes, 40.0 mL, 101 mmol) was added dropwise to a solution of ethyl 2-(diethoxyphosphoryl)acetate **151** (22.0 g, 106 mmol)) in THF (150 mL) at –78 ºC. After 30 min, a solution of pivalaldehyde (10.0 mL, 92.0 mmol) in THF (150 mL) was added *via* cannula and the mixture stirred overnight. Reaction was quenched with saturated ammonium chloride solution (250 mL) and the resulting biphasic mixture extracted with dichloromethane (250 mL). The organic layer was washed with brine (250 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude (*E*)-ethyl 4,4-dimethylpent-2-enoate **155** (13.3 g) as a yellow oil with spectroscopic data in accordance with the literature.[150] Product was used without further purification.

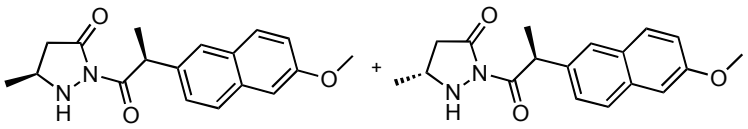
$\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 6.97 (1H, d, *J* 15.9, C*H*CHCO$_2$), 5.73 (1H, d, *J* 15.9, C*H*CO$_2$), 4.19 (2H, q, *J* 7.1, OCH_2CH$_3$), 1.29 (3H, t, *J* 7.1, OCH$_2$CH_3) and 1.08 (9H, s, C(CH_3)$_3$).

To a solution of hydrazine hydrate (5.00 mL, 101 mmol) in absolute ethanol (140 mL) was added crude (*E*)-ethyl 4,4-dimethylpent-2-enoate **155** (13.3 g, 85.1 mmol) and the resulting solution stirred at reflux overnight before concentration *in vacuo*. The crude oil was then purified by trituration in diethyl ether followed by filtration to give 3.68 g of the title compound as a colourless solid. The filtrate was concentrated *in vacuo* and purified by column

chromatography on silica gel, eluting with 8 % methanol in dichloromethane to give a further 3.20 g of the title compound (6.68 g in total, 53 % combined yield).

$\boldsymbol{\nu}_{\mathbf{max}}$ (KBr disc)/ cm^{-1} $\boldsymbol{\nu}_{\mathbf{max}}$ (KBr disc)/ cm^{-1} 3270 (N-H), 3219 (N-H), 2958 (C-H), 2870 (C-H) and 1667 (C=O); ***mp*** 85–89 ˚C; $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 4.95 (2H, bs, N(1)*H* and N(2)*H*), 3.47 (1H, app t, *J* 8.6, C(5)*H*), 2.45 (1H, dd, ABX system, J_{AB} 16.7, J_{AX} 8.2, C(4)H_AH_B), 2.38 (1H, dd, ABX system, J_{BA} 16.7, J_{BX} 8.9, C(4)H_AH_B) and 0.95 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 176.8 (*C*(3)O), 67.5 (*C*(5)H), 33.1 (*C*(4)H_2), 33.0 (*C*(CH_3)$_3$) and 37.3 (C(*C*H_3)$_3$); ***m/z*** HRMS (ESI^+) $C_7H_{14}N_2ONa$ ($[M+Na]^+$) requires 165.1004, found 165.1001 (-1.7 ppm).

(*S*)-2-((*S*)-2'-(6-Methoxynaphthalen-2-yl)propanoyl)-5-methylpyrazolidin-3-one (5*S*)-157 and (*R*)-2-((*S*)-2'-(6-methoxynaphthalen-2-yl)propanoyl)-5-methylpyrazolidin-3-one (5*R*)-157

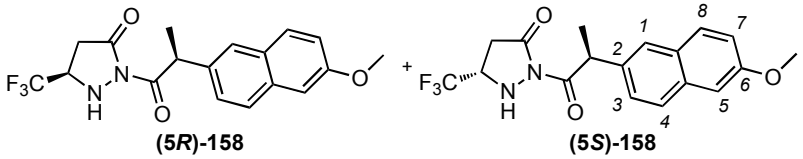


N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.91 g, 10.0 mmol), 1-hydroxybenzotriazole (1.35 g, 10.0 mmol), (*S*)-Naproxen (2.30 g, 10.0 mmol) and (*RS*)-5-methylpyrazolidin-3-one **71** (1.00 g, 10.0 mmol) were combined according to general procedure E. The crude material was purified by column chromatography, eluting with 80 % diethyl ether in petrol to give title compound **(5*S*)-157** (220 mg, 7 %) and 590 mg of mixed fractions (810 mg of compounds **(5*S*)-** and **(5*R*)-157** over all fractions, 26 % combined yield).

Compound (5*S*)-157 (upper spot): $\boldsymbol{[\alpha]^{20}_D}$ +11.3 (*c* 0.6, dichloromethane); $\boldsymbol{\nu}_{\mathbf{max}}$ (KBr disc)/ cm^{-1} 3249 (N-H), 2979 (Ar-H), 2955 (C-H), 2935 (C-H), 1769 (C=O), 1748 (C=O), 1669 (N-H bend) and 1605 (Ar C=C); ***mp*** 142–144 ˚C; $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.71–7.67 (3H, m, Ar*H*), 7.45 (1H, dd, *J* 8.5, 1.8, Ar*H*), 7.14–7.09 (2H, m, Ar*H*), 4.98 (1H, q, *J* 7.0, C*H*(CH_3)Ar), 4.97 (1H, br s, N(1)*H*), 3.90 (3H, s, OCH_3), 3.64–3.47 (1H, m, C(5)*H*), 2.67 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 6.7, C(4)H_AH_B), 2.41 (1H, dd, J_{BA} 17.0, J_{BX} 10.2, C(4)H_AH_B), 1.54 (3H, d, *J* 7.0, CH(CH_3)Ar) and 1.25 (3H, d, *J* 6.3, C(5)H(CH_3)); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 171.3 (*C*(O)), 171.2 (*C*(O)), 157.7 (O*C*Ar$_{ipso}$), 135.8 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.5 (*C*Ar), 129.0 (*C*Ar$_{ipso}$), 127.2 (*C*Ar), 127.0 (*C*Ar), 126.6 (*C*Ar), 119.0 (*C*Ar), 105.6 (*C*Ar), 55.4 (OCH_3), 49.8 (*C*(5)H), 44.3 (*C*H(CH_3)Ar), 42.2 (*C*(4)H_2), 19.4 (CH(*C*H_3)Ar) and 18.6

(C(5)H(CH_3)); ***m/z*** HRMS (ESI^+) $C_{18}H_{21}N_2O_3$ ($[M+H]^+$) requires 315.1547, found 315.1549 (+0.7 ppm).

(*S*)-2-((*S*)-2'-(6-Methoxynaphthalen-2-yl)propanoyl)-5-(trifluoromethyl)pyrazolidin-3-one (5*R*)-158 and (*R*)-2-((*S*)-2'-(6-methoxynaphthalen-2-yl)propanoyl)-5-(trifluoromethyl)-pyrazolidin-3-one (5*S*)-158

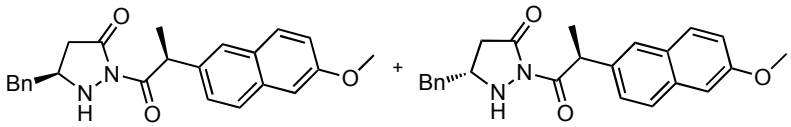


N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.55 g, 8.11 mmol), 1-hydroxybenzotriazole (1.10 g, 8.11 mmol), (*S*)-Naproxen (1.87 g, 8.11 mmol) and (*RS*)-5-(trifluoromethyl)pyrazolidin-3-one **84** (1.25 g, 8.11 mmol) were combined according to general procedure E. The crude material was purified by column chromatography, eluting with 25 % ethyl acetate in petrol then pure ethyl acetate to give impure fractions of title compound **(5*R*)-158** (766 mg) and fractions of title compound **(5*S*)-158** contaminated with residual (*S*)-Naproxen (474 mg). The fractions of **(5*R*)-158** were purified by recrystallisation in methanol and the minimum of ethyl acetate to give title compound **(5*R*)-158** as a colourless solid (229 mg, 8 %). The fractions of **(5*S*)-158** were taken up in dichloromethane (100 mL) and washed with saturated sodium bicarbonate solution (2 x 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give title compound **(5*S*)-158** as a colourless solid (219 mg, 7 %) (448 mg of compounds **(5*R*)-** and **(5*S*)-158** over all fractions, 15 % combined yield).

Compound (5*R*)-158 (upper spot): $[\alpha]^{20}_D$ +3.3 (*c* 0.6, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3259 (N-H), 2938 (C-H), 1760 (C=O), 1672 (C=O), 1635 (N-H bend) and 1610 (Ar C=C); ***mp*** 162–165 ˚C; δ_F (282 MHz, $CDCl_3$) –78.2 (3F, d, *J* 6.8, CF_3); δ_H (300 MHz, $CDCl_3$) 7.70–7.67 (3H, m, Ar*H*), 7.44 (1H, dd, *J* 8.5, 1.8, Ar*H*), 7.15–7.09 (2H, m, Ar*H*), 5.66 (1H, d, *J* 6.3, N(1)*H*), 4.99 (1H, q, *J* 7.0, C*H*(CH_3)), 4.00 (1H, app dsext, *J* 8.8, 6.6, C(5)*H*), 3.90 (3H, s, OCH_3), 3.00 (1H, dd, ABX system, J_{AB} 17.9, J_{AX} 8.8, C(4)$H_A$$H_B$), 2.91 (1H, dd, J_{BA} 17.9, J_{BX} 6.3, C(4)$H_A$$H_B$) and 1.57 (3H, d, *J* 7.0, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 170.8 (N(2)*C*(O)), 167.0 (*C*(3)O), 157.8 (O*C*Ar$_{ipso}$), 135.1 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.4 (*C*Ar), 128.9 (*C*Ar$_{ipso}$), 127.2 (*C*Ar), 126.9 (*C*Ar), 126.8 (*C*Ar), 124.3 (q, *J* 280, *C*F_3), 119.1 (*C*Ar), 105.6 (*C*Ar), 55.4 (O*C*H_3), 52.8 (q, *J* 32.5, *C*(5)H), 43.9 (*C*H(CH_3)), 33.8 (*C*(4)H_2) and 19.3 (CH(*C*H_3));

m/z HRMS (ESI^+) $C_{18}H_{17}N_2O_3F_3Na$ ($[M+Na]^+$) requires 389.1089, found 389.1094 (+1.2 ppm). **Compound (5*S*)-158** (lower spot): $[\alpha]^{20}_D$ +18.5 (*c* 0.5, acetonitrile); ν_{max} (KBr disc)/ cm^{-1} 3292 (N-H), 2988 (C-H), 2944 (C-H), 1757 (C=O), 1677 (C=O), 1631 (N-H bend) and 1605 (Ar C=C); ***mp*** 161–162 ˚C; δ_F (282 MHz, $(CD_3)_2S(O)$) –77.5 (3F, d, *J* 8.2, CF_3); δ_H (300 MHz, $(CD_3)_2S(O)$) 7.78 (1H, d, *J* 9.0, CAr(8)*H*), 7.76 (1H, d, *J* 8.6, CAr(4)*H*), 7.60 (1H, d, *J* 1.6, CAr(1)*H*), 7.33 (1H, dd, *J* 8.6, 1.6, CAr(3)*H*), 7.27 (1H, d, *J* 2.4, CAr(5)*H*), 7.14 (1H, dd, *J* 9.0, 2.4, CAr(7)*H*), 6.87 (1H, d, *J* 7.2, N(1)*H*), 4.88 (1H, q, *J* 6.8, C*H*(CH_3)), 4.35–4.22 (1H, m, C(5)*H*), 3.86 (3H, s, OCH_3), 3.25 (1H, dd, ABX system, J_{AB} 18.3, J_{AX} 10.1, C(4)$H_A$$H_B$), 2.67 (1H, dd, J_{BA} 18.3, J_{BX} 2.7, C(4)$H_A$$H_B$) and 1.42 (3H, d, *J* 6.8, CH(CH_3)); δ_C (75 MHz, $(CD_3)_2S(O)$) 170.7 (N(2)*C*(O)), 170.5 (*C*(3)O), 157.6 (O*C*Ar_{ipso}), 136.0 (*C*Ar_{ipso}), 133.6 (*C*Ar_{ipso}), 129.5 (*C*Ar), 128.7 (*C*Ar_{ipso}), 127.3 (*C*Ar), 126.9 (*C*Ar), 126.0 (*C*Ar), 125.6 (q, *J* 280, *C*F_3), 119.1 (*C*Ar), 106.0 (*C*Ar), 55.5 (O*C*H_3), 51.9 (q, *J* 30.7, *C*(5)H), 43.8 (*C*H(CH_3)), 33.6 (*C*(4)H_2) and 19.2 (CH(*C*H_3)); ***m/z*** HRMS (ESI^+) $C_{18}H_{17}N_2O_3F_3Na$ ($[M+Na]^+$) requires 389.1089, found 389.1094 (+1.2 ppm).

(*S*)-2-((*S*)-2'-(6-Methoxynaphthalen-2-yl)propanoyl)-5-benzylpyrazolidin-3-one (5*S*)-159 and (*R*)-2-((*S*)-2'-(6-methoxynaphthalen-2-yl)propanoyl)-5-benzylpyrazolidin-3-one (5*R*)-159



(5*S*)-159 **(5*R*)-159**

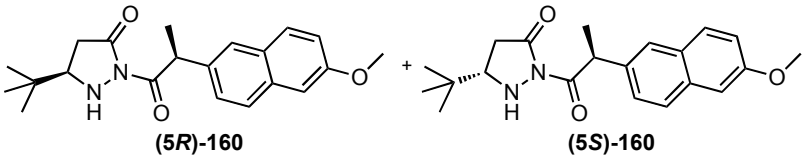
N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (3.27 g, 17.0 mmol), 1-hydroxybenzotriazole (2.30 g, 17.0 mmol), (*S*)-Naproxen (3.93 g, 17.0 mmol) and (*RS*)-5-benzylpyrazolidin-3-one **153** (3.00 g, 17.0 mmol) were combined according to general procedure E. The crude material was dissolved in diethyl ether and a minimum of dichloromethane, cooled to 0 ºC overnight and the resulting mixture filtered to give title compound **(5*S*)-159** as a colourless solid (1.20 g, 18 %). The filtrate was concentrated *in vacuo* and taken up in diethyl ether and a minimum of methanol. 560 mg of colourless solid composed of a 14:86 mixture of title compounds **(5*S*)-** and **(5*R*)-159** respectively, was collected (1.76 g of compounds **(5*S*)-** and **(5*R*)-159** over all fractions, 27 % combined yield). In order to access pure compound **(5*R*)-159**, this mixture was subjected to recrystallisation from methanol and the

minimum quantity of dichloromethane to give title compound **(5*R*)-159** as a colourless solid (342 mg, 5 %).

Compound (5*S*)-159 (upper spot): $[\alpha]^{20}_D$ +31.2 (*c* 0.3, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3265 (N-H), 3060 (Ar-H), 2976 (C-H), 2935 (C-H), 1723 (C=O), 1687 (C=O), 1630 (N-H bend) and 1605 (Ar C=C); ***mp*** 147–148 ˚C; δ_N ($CDCl_3$) 193 (*N*(2)C(O)), 103 (*N*(1)H); δ_H (500 MHz, $CDCl_3$) 7.70–7.68 (3H, m, Ar*H*), 7.45 (1H, dd, *J* 8.5, 1.3, Ar*H*), 7.33–7.25 (3H, m, Ar*H*), 7.16–7.10 (4H, m, Ar*H*), 5.19 (1H, br s, N(1)*H*), 4.98 (1H, q, *J* 6.9, C*H*(CH_3)), 3.91 (3H, s, OCH_3), 3.69 (1H, app dq, *J* 9.4, 6.7, C(5)*H*), 2.89 (1H, dd, ABX system, J_{AB} 13.7, J_{AX} 6.8, C$H_A$$H_B$Ph), 2.83 (1H, dd, J_{BA} 13.7, J_{BX} 6.3, CH_AH_BPh), 2.64 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 6.9, C(4)$H_A$$H_B$), 2.55 (1H, dd, J_{BA} 17.0, J_{BX} 9.4, C(4)$H_A$$H_B$) and 1.56 (3H, d, *J* 6.8, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 170.9 (N(2)*C*(O)), 170.1 (*C*(3)O), 157.8 (O*C*Ar_{ipso}), 136.4 (*C*Ar_{ipso}), 135.8 (*C*Ar_{ipso}), 133.8 (*C*Ar_{ipso}), 129.5 (*C*Ar), 129.2 (*C*Ar), 129.1 (*C*Ar_{ipso}), 129.0 (*C*Ar), 127.3 (*C*Ar), 127.2 (*C*Ar), 126.9 (*C*Ar), 126.6 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 55.4 (O*C*H_3), 55.0 (*C*(5)H), 44.1 (*C*H(CH_3)), 40.1 (*C*H_2Ph), 39.6 (*C*(4)H_2) and 19.4 (CH(*C*H_3)); ***m/z*** HRMS (ESI^+) $C_{24}H_{24}N_2O_3Na$ ($[M+Na]^+$) requires 411.1685, found 411.1675 (–2.4 ppm).

Compound (5*R*)-159 (lower spot): $[\alpha]^{20}_D$ +68.0 (*c* 0.5, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3241 (N-H), 2970 (C-H), 2946 (C-H), 1769 (C=O), 1682 (C=O), 1629 (N-H bend) and 1604 (Ar C=C); ***mp*** 133–134 ˚C; δ_H (300 MHz, $CDCl_3$) 7.71–7.68 (3H, m, Ar*H*), 7.44 (1H, dd, *J* 8.4, 1.9, Ar*H*), 7.30–7.21 (3H, m, Ar*H*), 7.15–7.06 (4H, m, Ar*H*), 4.99 (1H, q, *J* 7.0, C*H*(CH_3)), 3.91 (3H, s, OCH_3), 3.79 (1H, app quin, *J* 7.3, C(5)*H*), 2.79 (1H, dd, ABX system, J_{AB} 13.8, J_{AX} 7.4, C$H_A$$H_B$Ph), 2.75 (1H, dd, ABX system, J_{AB} 17.0, J_{AX} 7.0, C(4)$H_A$$H_B$), 2.70 (1H, dd, J_{BA} 13.8, J_{BX} 6.7, CH_AH_BPh), 2.48 (1H, dd, J_{BA} 17.0, J_{BX} 8.4, C(4)$H_A$$H_B$) and 1.54 (3H, d, *J* 7.0, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 170.9 (N(2)*C*(O)), 170.1 (*C*(3)O), 157.8 (O*C*Ar_{ipso}), 136.6 (*C*Ar_{ipso}), 135.6 (*C*Ar_{ipso}), 133.8 (*C*Ar_{ipso}), 129.5 (*C*Ar), 129.1 (*C*Ar), 129.0 (*C*Ar_{ipso}), 128.9 (*C*Ar), 127.24 (*C*Ar), 127.21 (*C*Ar), 127.0 (*C*Ar), 126.7 (*C*Ar), 119.0 (*C*Ar), 105.7 (*C*Ar), 55.5 (O*C*H_3 & *C*(5)H), 44.1 (*C*H(CH_3)), 40.1 (*C*(4)H_2), 39.7 (*C*H_2Ph) and 19.4 (CH(*C*H_3)); ***m/z*** HRMS (ESI^+) $C_{24}H_{25}N_2O_3$ ($[M+H]^+$) requires 389.1860, found 389.1858 (–0.4 ppm).

(*R*)-2-((*S*)-2'-(6-Methoxynaphthalen-2-yl)propanoyl)-5-(*tert*-butyl)-pyrazolidin-3-one (5*R*)-160 and (*S*)-2-((*S*)-2'-(6-methoxynaphthalen-2-yl)propanoyl)-5-(*tert*-butyl)-pyrazolidin-3-one (5*S*)-160

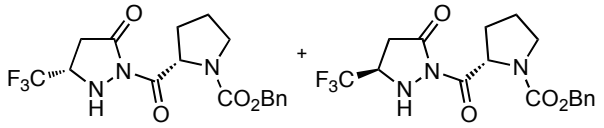


N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (5.03 g, 25.9 mmol), 1-hydroxybenzotriazole (3.56 g, 25.9 mmol), (*S*)-Naproxen (6.00 g, 25.9 mmol) and (*RS*)-5-(*tert*-butyl)pyrazolidin-3-one **156** (3.68 g, 25.9 mmol) were combined according to general procedure E. The crude material was partially purified by column chromatography on silica gel, eluting with 60 % diethyl ether in petrol to give first 700 mg of fractions enriched in title compound **(5*R*)-160** (**(5*R*)**:**(5*S*)** 85:15) then 710 mg of fractions enriched in title compound **(5*S*)-160** (**(5*R*)**:**(5*S*)** 9:91). 2.24 g of mixed fractions were also collected (**(5*R*)**:**(5*S*)** 42:58) (3.65 g of compounds **(5*R*)-160** and **(5*S*)-160** over all fractions, 40 % combined yield). The fractions enriched in title compound **(5*R*)-160** were further purified by column chromatography on silica gel, eluting with 40 % diethyl ether in petrol to give title compound **(5*R*)-160** as an amorphous white solid (360 mg, 4 %) and 300 mg of mixed fractions. The fractions enriched in title compound **(5*S*)-160** were further purified by dissolution in diethyl ether followed by cooling to 0 ºC. Collection by filtration then gave title compound **(5*S*)-160** as a colourless solid (264 mg, 3 %).

Compound (5*R*)-160 (upper spot): $[\alpha]^{20}_{D}$ –1.0 (*c* 0.5, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3281 (N-H), 2960 (C-H), 2931 (C-H), 1744 (C=O), 1678 (C=O), 1631 (N-H bend) and 1607 (Ar C=C); ***mp*** 45–46 ˚C; δ_H (300 MHz, $CDCl_3$) 7.73–7.67 (3H, m, Ar*H*), 7.47 (1H, dd, *J* 8.5, 1.8, Ar*H*), 7.14–7.09 (2H, m, Ar*H*), 5.27 (1H, br s, N(1)*H*), 5.04 (1H, q, *J* 7.0, C*H*(CH_3)), 3.91 (3H, s, OCH_3), 3.21 (1H, dd, *J* 11.3, 7.6, C(5)*H*), 2.63 (1H, dd, ABX system, J_{AB} 17.2, J_{AX} 11.3, C(4)H_AH$_B$), 2.50 (1H, dd, J_{BA} 17.2, J_{BX} 7.6, C(4)H$_A$$H_B$), 1.56 (3H, d, *J* 7.0, CH(CH_3)) and 0.92 (9H, s, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 170.8 (N(2)*C*(O)), 170.2 (*C*(3)O), 157.7 (O*C*Ar$_{ipso}$), 135.9 (*C*Ar$_{ipso}$), 133.8 (*C*Ar$_{ipso}$), 129.4 (*C*Ar), 129.0 (*C*Ar$_{ipso}$), 127.1 (*C*Ar), 127.0 (*C*Ar), 126.6 (*C*Ar), 119.0 (*C*Ar), 105.6 (*C*Ar), 62.3 (*C*(5)H), 55.4 (O*C*H$_3$), 43.9 (*C*H(CH$_3$)), 35.9 (*C*(4)H$_2$), 32.4 (*C*(CH$_3$)$_3$), 25.7 (C(*C*H$_3$)$_3$) and 19.4 (CH(*C*H$_3$)); ***m/z*** HRMS (ESI^+) $C_{21}H_{27}N_2O_3$ ($[M+H]^+$) requires 355.2016, found 355.2015 (–0.3 ppm).

Compound (5*S*)-160 (lower spot): $[\alpha]^{20}_D$ +28.2 (*c* 0.5, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3290 (N-H), 2869 (C-H), 1741 (C=O), 1679 (C=O), 1634 (N-H bend) and 1606 (Ar C=C); ***mp*** 86–87 °C; δ_H (300 MHz, $CDCl_3$) 7.71–7.66 (3H, m, Ar*H*), 7.46 (1H, dd, *J* 8.5, 1.8, Ar*H*), 7.14–7.08 (2H, m, Ar*H*), 5.35 (1H, br s, N(1)*H*), 5.03 (1H, q, *J* 6.9, C*H*(CH_3)), 3.90 (3H, s, OCH_3), 3.26 (1H, dd, *J* 10.1, 8.0, C(5)*H*), 2.58 (1H, dd, ABX system, J_{AB} 17.2, J_{AX} 8.0, C(4)H_AH_B), 2.51 (1H, dd, J_{BA} 17.2, J_{BX} 10.1, C(4)H_AH_B), 1.56 (3H, d, *J* 6.9, CH(CH_3)) and 0.85 (9H, s, C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 170.6 (N(2)*C*(O)), 170.4 (*C*(3)O), 157.7 (O*C*Ar$_{ipso}$), 135.5 (*C*Ar$_{ipso}$), 133.7 (*C*Ar$_{ipso}$), 129.4 (*C*Ar), 129.0 (*C*Ar$_{ipso}$), 127.1 (*C*Ar), 127.0 (*C*Ar), 126.6 (*C*Ar), 118.9 (*C*Ar), 105.6 (*C*Ar), 62.7 (*C*(5)H), 55.4 (OCH_3), 43.9 (*C*H(CH_3)), 35.9 (*C*(4)H_2), 32.7 (*C*(CH_3)$_3$), 25.7 (C(*C*H_3)$_3$) and 19.4 (CH(*C*H_3)); ***m/z*** HRMS (ESI^+) $C_{21}H_{26}N_2O_3Na$ ($[M+Na]^+$) requires 377.1841, found 377.1826 (–4.0 ppm).

(*S*)-2-((*S*)-1'-((benzyloxy)carbonyl)pyrrolidine-2'-carbonyl)-5-(trifluoromethyl) pyrazolidin-3-one (5*S*)-163 and (*R*)-2-((*S*)-1'-((benzyloxy)carbonyl)pyrrolidine-2'-carbonyl)-5-(trifluoromethyl)pyrazolidin-3-one (5*R*)-163



(5*S*)-163 **(5*R*)-163**

N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.57 g, 8.21 mmol), 1-hydroxybenzotriazole (1.10 g, 8.21 mmol), crude (*S*)-*N*-(benzyloxycarbonyl)-proline **141** (1.87 g, 9.03 mmol, added as solution in 5 mL DMF) and (*RS*)-5-(trifluoromethyl)pyrazolidin-3-one **84** (1.26 g, 8.21 mmol) were combined according to general procedure E. The crude material was purified by column chromatography, eluting with 85 % diethyl ether in petrol to give title compound **(5*S*)-163** as a colourless oil (305 mg, 10 %) and fractions containing title compound **(5*R*)-163** and a minor impurity (286 mg). 135 mg of mixed fractions were also collected. The fractions containing title compound **(5*R*)-163** were purified by further column chromatography, eluting with 60 % ethyl acetate in petrol to give title compound **(5*R*)-163** as a colourless foam (190 mg, 6 %) (630 mg of compounds **(5*S*)-** and **(5*R*)-163** over all fractions, 20 % combined yield).

Compound (5*S*)-163 (upper spot): $[\alpha]^{20}_D$ –46.1 (*c* 0.6, chloroform); ν_{max} (KBr disc)/ cm^{-1} 3256 (N-H), 3064 (Ar-H), 3034 (Ar-H), 2980 (C-H), 2957 (C-H), 1786 (C=O), 1757 (C=O), 1707 (C=O) and 1587 (N-H bend); δ_F (376 MHz, $CDCl_3$, rotamers A:B 1.5:1) –78.2 (B, 3F, d,

J 6.5, C*F*$_3$), –78.3 (A, 3F, d, *J* 6.6, C*F*$_3$); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$, rotamers A:B 1.5:1) 7.42–7.27 (A, 5H, m, Ar*H* & B, 5H, m, Ar*H*), 5.85 (A, 1H, d, *J* 7.2, N(1)*H*), 5.34–5.28 (A, 1H, m, $N_{Pro}CH$ & B, 2H, m, $N_{Pro}CH$ & N(1)*H*), 5.14 (A, 1H, d, AB system, J_{AB} 12.6, PhCH_AH_B), 5.13 (B, 1H, d, AB system, J_{AB} 12.1, PhCH_AH_B), 5.11 (A, 1H, d, AB system, J_{BA} 12.6, PhCH_AH_B), 4.94 (B, 1H, d, AB system, J_{BA} 12.1, PhCH_AH_B), 4.21–4.07 (A, 1H, m, C(5)*H*), 3.74–3.47 (A, 2H, m, $N_{Pro}CH_2$ & B, 3H, m, $N_{Pro}CH_2$ & C(5)*H*), 3.19 (A, 1H, dd, ABX system, J_{AB} 18.0, J_{AX} 9.6, C(4)H_AH_B), 2.88 (A, 1H, dd, ABX system, J_{BA} 18.0, J_{BX} 5.2, C(4)H_AH_B), 2.75 (B, 1H, d, *J* 7.4, C(4)H_2), 2.37–2.27 (A, 1H, m, $N_{Pro}CHCH_AH_B$ & B, 1H, m, $N_{Pro}CHCH_AH_B$) and 2.03–1.86 (A, 3H, m, $N_{Pro}CHCH_AH_BCH_2$ & B, 3H, m, $N_{Pro}CHCH_AH_BCH_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.6 (N(2)*C*(O)), 168.3 (N(2)*C*(O)), 168.9 (*C*(3)O), 168.5 (*C*(3)O), 155.1 (*C*(O)O), 154.1 (*C*(O)O), 136.9 (*C*Ar$_{ipso}$), 136.7 (*C*Ar$_{ipso}$), 128.7 (2 x *C*Ar), 128.6 (*C*Ar), 128.3 (*C*Ar), 128.1 (*C*Ar), 127.4 (*C*Ar), 124.5 (q, *J* 279, *C*F_3), 124.2 (q, *J* 279, *C*F_3), 67.2 (*C*H_2Ph), 67.1 (*C*H_2Ph), 59.9 ($N_{Pro}CH$), 58.8 ($N_{Pro}CH$), 53.3 (q, *J* 32.6, *C*(5)H), 53.2 (q, *J* 33.0, *C*(5)H), 47.3 ($N_{Pro}CH_2$), 47.0 ($N_{Pro}CH_2$), 33.5 (*C*(4)H_2), 33.4 (*C*(4)H_2), 30.5 ($N_{Pro}CHCH_2CH_2$), 29.7 ($N_{Pro}CHCH_2CH_2$), 24.0 ($N_{Pro}CHCH_2CH_2$) and 23.4 ($N_{Pro}CHCH_2CH_2$); ***m/z*** HRMS (ESI^+) $C_{17}H_{19}N_3O_4F_3$ ($[M+H]^+$) requires 386.1323, found 386.1322 (+0.9 ppm).

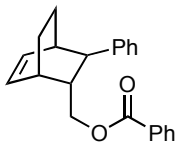
Compound (5*R*)-163 (lower spot): $\boldsymbol{[\alpha]^{20}_D}$ –34.1 (*c* 0.5, chloroform); ***mp*** 50 °C; $\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3240 (N-H), 3036 (Ar-H), 2985 (C-H), 2957 (C-H), 2886 (C-H), 1786 (C=O), 1761 (C=O) and 1701 (C=O); $\boldsymbol{\delta_N}$ (CD_3OD) 184 (*N*(2)C(O)), 97.6 (*N*$_{Pro}$C(O)O), 86.4 (*N*(1)H); $\boldsymbol{\delta_F}$ (282 MHz, $(CD_3)_2S(O)$), ^{1}H decoupled, rotamers A:B 1.1:1) –77.3 (A, 3F, s, C*F*$_3$), –77.5 (B, 3F, s, C*F*$_3$); $\boldsymbol{\delta_H}$ (300 MHz, $(CD_3)_2S(O)$, rotamers A:B 1.1:1) 7.38–7.19 (A, 5H, m, Ar*H* & B, 5H, m, Ar*H*), 6.92 (B, 1H, d, *J* 8.6, N(1)*H*), 6.89 (A, 1H, d, *J* 7.8, N(1)*H*), 5.14 (B, 1H, dd, *J* 8.7, 2.5, $N_{Pro}CH$), 5.07 (A, 2H, s, PhCH_2), 5.03 (A, 1H, dd, *J* 8.9, 1.9, $N_{Pro}CH$), 4.98 (B, 2H, s, PhCH_2), 4.45–4.31 (A, 1H, m, C(5)*H* & B, 1H, m, C(5)*H*), 3.49–3.27 (A, 3H, m, $N_{Pro}CH_2$ & C(4)H_AH_B & B, 3H, m, $N_{Pro}CH_2$ & C(4)H_AH_B), 2.81 (B, 1H, dd, ABX system, J_{BA} 18.3, J_{BX} 3.1, C(4)H_AH_B), 2.78 (A, 1H, dd, ABX system, J_{BA} 18.4, J_{BX} 3.0, C(4)H_AH_B), 2.35–2.16 (A, 1H, m, $N_{Pro}CHCH_AH_B$ & B, 1H, m, $N_{Pro}CHCH_AH_B$) and 1.93–1.69 (A, 3H, m, $N_{Pro}CHCH_AH_BCH_2$ & B, 3H, m, $N_{Pro}CHCH_AH_BCH_2$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 169.7 (N(2)*C*(O)), 169.6 (N(2)*C*(O)), 169.4 (*C*(3)O), 169.0 (*C*(3)O), 154.9 (*C*(O)O), 154.1 (*C*(O)O), 136.6 (*C*Ar$_{ipso}$), 136.5 (*C*Ar$_{ipso}$), 128.6 (*C*Ar), 128.5 (*C*Ar), 128.0 (*C*Ar), 127.9 (*C*Ar), 127.6 (*C*Ar), 124.6 (q, *J* 279, *C*F_3), 124.5 (q, *J* 279, *C*F_3), 67.2 (*C*H_2Ph), 67.1 (*C*H_2Ph), 59.7 ($N_{Pro}CH$), 59.2 ($N_{Pro}CH$), 53.3 (q, *J* 32.3, *C*(5)H), 53.2 (q, *J* 32.6, *C*(5)H), 47.3 ($N_{Pro}CH_2$), 47.0 ($N_{Pro}CH_2$), 33.3 (*C*(4)H_2), 33.1 (*C*(4)H_2), 30.6 ($N_{Pro}CHCH_2CH_2$), 29.5 ($N_{Pro}CHCH_2CH_2$), 24.0 ($N_{Pro}CHCH_2CH_2$)

and 23.0 ($N_{Pro}CHCH_2CH_2$); ***m/z*** HRMS (ESI^+) $C_{17}H_{22}N_4O_4F_3$ ($[M+NH_4]^+$) requires 403.1599, found 403.1589 (–2.4 ppm).

Upon heating to 100 ˚C, the observed rotamers coalesced:

$\boldsymbol{\delta_F}$ (282 MHz, $(CD_3)_2S(O)$, ^1H decoupled) –77.1 (3F, s, CF_3); $\boldsymbol{\delta_H}$ (300 MHz, $(CD_3)_2S(O)$) 7.36–7.26 (5H, m, Ar*H*), 6.74 (1H, d, *J* 7.4, N(1)*H*), 5.13 (1H, d, *J* 9.5, $N_{Pro}CH$), 5.05 (1H, s, $PhCH_2$), 4.41–4.26 (1H, m, C(5)*H*), 3.49 (2H, app t, *J* 6.8, $N_{Pro}CH_2$), 3.30 (1H, dd, ABX system, J_{AB} 18.1, J_{AX} 9.9, $C(4)H_AH_B$), 2.75 (1H, dd, ABX system, J_{BA} 18.1, J_{BX} 3.6, $C(4)H_AH_B$), 2.36–2.21 (1H, m, $N_{Pro}CHCH_AH_B$) and 1.94–1.78 (3H, m, $N_{Pro}CHCH_AH_BCH_2$).

endo-(1*SR*,2*RS*,3*RS*,4*RS*)-3-Phenylbicyclo[2.2.2]oct-5-en-2-yl)methyl benzoate *endo*-164



***endo*-164**

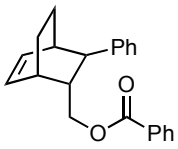
Following the method of Deutsch, *et al.*,[151] a solution of (*E*)-cinnamaldehyde **37** (0.250 mL, 2.00 mmol), cyclohexadiene (200 mg, 2.50 mmol) and 2 crystals of hydroquinone in toluene (0.2 mL) in a sealed tube was flushed with nitrogen then heated at 160 ºC for 2 days. ^1H NMR spectroscopic analysis indicated reaction had achieved 40 % conversion (*exo*:*endo* 67:33). The crude material was then purified by column chromatography, eluting with 7.5 % diethyl ether in petrol to yield *endo*-(1*SR*,2*RS*,3*RS*,4*RS*)-phenylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde ***endo*-118** as a colourless oil, with spectroscopic data in accordance with the literature (32 mg, 8 %).[85]

endo-(1*SR*,2*RS*,3*RS*,4*RS*)-Phenylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde ***endo*-118** (32.0 mg, 0.150 mmol), sodium borohydride (17.0 mg, 0.450 mmol), triethylamine (30.0 µL, 0.216 mmol), DMAP (18.0 mg, 0.150 mmol) and benzoyl chloride (20.0 µL, 0.175 mmol) were combined according to general procedure F. The crude material was purified by column chromatography on silica gel, eluting with 2 % diethyl ether in petrol to give the title compound as a colourless solid (28 mg, 58 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 2931 (C-H), 2867 (C-H), 1711 (C=O), 1658 (Ar C=C) and 1601 (Ar C=C); ***mp*** 73–75 ˚C; $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.81 (2H, dd, *J* 8.3, 1.4, Ar*H*), 7.50 (1H, tt, *J* 7.4, 1.4, Ar*H*), 7.37–7.32 (5H, m, Ar*H*), 7.27–7.19 (2H, m, Ar*H*), 6.53 (1H, app t, *J* 7.4, CH_A=CH_B), 6.25 (1H, app t, *J* 7.3, CH_A=CH_B), 4.08 (1H, dd, ABX system, J_{AB} 10.6, J_{AX} 8.2, CH_AH_BO), 3.96 (1H, dd, ABX system, J_{BA} 10.6, J_{BX} 6.6, CH_AH_BO), 2.80–2.75 (1H, m, C*H*Ph),

2.51–2.39 (3H, m, C*H*C*H*CH_2O & C*H*CHPh), 1.74–1.68 (2H, m, CH_AH_BCHCHCHO & CH_AH_BCHCHPh), 1.49–1.41 (1H, m, CH_AH_BCHCHCHO) and 1.12–1.00 (1H, m, CH_AH_BCHCHPh); δ_C (75 MHz, $CDCl_3$) 203.5 (*C*HO), 139.1 (*C*H_A=CH_B), 136.9 (*C*Ar_{ipso}), 135.9 (*C*Ar_{ipso}), 134.2 (CH_A=*C*H_B), 132.5 (*C*Ar_{ipso}), 129.0 (*C*Ar), 127.3 (*C*Ar), 126.3 (*C*Ar), 125.8 (*C*Ar), 125.4 (*C*Ar), 123.8 (*C*Ar), 123.0 (*C*Ar), 59.1 (*C*HCHO), 49.7 (*C*HCH_2), 47.6 (*C*H_2), 45.7 (*C*HCH_2) and 41.4 (*C*HAr); ***m/z*** HRMS (ESI^+) $C_{22}H_{26}NO_2$ ($[M+NH_4]^+$) requires 336.1958, found 336.1963 (+1.5 ppm).

endo-(1*S*,2*R*,3*R*,4*R*)-3-Phenylbicyclo[2.2.2]oct-5-en-2-yl)methyl benzoate _endo_-(2*R*)-164



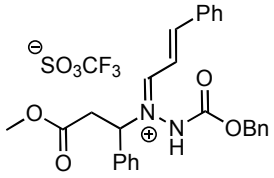
***endo*-(2*R*)-164**

endo-(1*S*,2*R*,3*R*,4*R*)-Phenylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde ***endo*-(2*R*)-118** (31.0 mg, 0.146 mmol), sodium borohydride (17.0 mg, 0.450 mmol), triethylamine (30.0 μL, 0.216 mmol), DMAP (18.0 mg, 0.150 mmol) and benzoyl chloride (20.0 μL, 0.175 mmol) were combined according to general procedure F. The crude material was purified by column chromatography on silica gel, eluting with 5 % diethyl ether in petrol to give the title compound as a colourless solid with an enantiomeric excess of 85 % (22 mg, 47 %).

$[\alpha]^{20}_D$ –10.6 (*c* 0.5, chloroform); ***mp*** 82–84 ˚C.

Enantiomeric excess was determined by HPLC with ChiralCel OJ-H column (0.5% isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 211 nm), t_R(2*S*) 15.3 min and t_R(2*R*) 24.7 min.

(*Z*)-Iminium ion of (*RS*)-benzyl 2-(3-methoxy-3-oxo-1-phenylpropyl)hydrazinecarboxylate trifluoromethanesulfonate 169



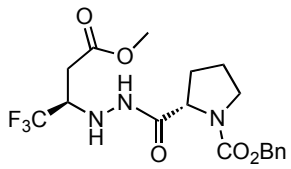
169

To a solution of benzyl 5-oxo-3-phenylpyrazolidine-1-carboxylate **114** (100 mg, 0.337 mmol) in dichloromethane (1 mL) was added triflic acid (42.0 μL, 0.337 mmol) and the mixture stirred at room temperature for 2 h. Upon addition of petrol, 105 mg of the triflate salt **168** precipitated

as a colourless solid and was collected by filtration. This solid was taken up in dry methanol (2 mL) and (*E*)-cinnamaldehyde **37** (35.0 μL, 0.260 mmol) added. The resulting mixture was left to stir at room temperature with occasional sampling and analysis by ^{1}H NMR spectroscopy to monitor reaction progress. After 3 weeks, the resultant dark red oil was triturated in diethyl ether and a minimum of dichloromethane to precipitate 10 mg of the title compound as a yellow solid. The filtrate was concentrated *in vacuo* and trituration repeated to yield a further 3 mg of title compound (13 mg in total, 9 %).

$\boldsymbol{\nu}_{\mathbf{max}}$ (KBr disc)/ cm^{-1} 3427 (N-H), 2925 (C-H), 2854 (C-H), 1751 (C=O), 1732 (C=O), 1613 (N-H bend) and 1588 (Ar C=C); ***mp*** 114-116 ºC; $\boldsymbol{\delta_F}$ (376 MHz, CD_3CN) –79.9 (3H, s, SO_3CF_3); $\boldsymbol{\delta_H}$ (300 MHz, CD_3CN) 9.08 (1H, d, *J* 10.2, C(N)*H*)), 8.96 (1H, br s, N*H*), 8.29 (1H, d, *J* 15.4, C(N)HCHC*H*), 7.81 (2H, d, *J* 7.4, Ar*H*), 7.73–7.68 (1H, m, Ar*H*), 7.59–7.31 (12H, m, Ar*H*), 7.07 (1H, dd, *J* 15.4, 10.2, C(N)HC*H*), 5.81 (1H, dd, *J* 10.1, 4.4, C*H*CH_2), 5.07 (2H, bs, CH_2Ph), 3.67 (3H, s, OCH_3), 3.48 (1H, dd, ABX system, J_{AB} 17.9, J_{AX} 10.1, C(O)H_AH$_B$) and 3.16 (1H, dd, ABX system, J_{BA} 17.9, J_{BX} 4.4, C(O)CH$_A$$H_B$); $\boldsymbol{\delta_C}$ (125 MHz, CD_3CN) 174.1 (*C*(N)), 170.9 (*C*(O)CH_3), 167.8 (C(N)CH*C*H), 134.0 (*C*Ar$_{ipso}$), 132.7 (*C*Ar$_{ipso}$), 136.4 (*C*Ar), 132.4 (*C*Ar), 131.3 (*C*Ar), 130.5 (*C*Ar), 130.0 (2x*C*Ar), 129.5 (*C*Ar), 129.2 (*C*Ar), 117.0 (C(N)*C*H), 72.6 (*C*HCH_2), 69.6 (*C*H_2Ph), 52.9 (OCH_3) and 34.9 (C(O)*C*H_2); ***m/z*** HRMS (ESI$^+$) $C_{27}H_{27}N_2O_4$ ([M-OTf]$^+$) requires 443.1965, found 443.1966 (+0.1 ppm).

(*R*)-Methyl 3-(2-((S)-1'-((benzyloxy)carbonyl)pyrrolidine-2'-carbonyl)hydrazinyl)-4,4,4-trifluorobutanoate 170

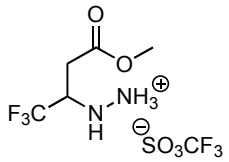


170

To a solution of (*S*)-benzyl 2-((*S*)-3-oxo-5-(trifluoromethyl)pyrazolidine-2-carbonyl)pyrrolidine-1-carboxylate **(5*R*)-163** (300 mg, 0.779 mmol) in methanol (5 mL) was added triflic acid (0.140 mL, 1.56 mmol) and the resulting mixture stirred at rt overnight. The excess acid was then quenched with saturated sodium hydrogen carbonate solution (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel, eluting with 60 % ethyl acetate in petrol to give the title compound as a colourless solid (120 mg, 39 %).

$[\alpha]^{20}_D$ –33.2 (*c* 0.5, methanol); ***mp*** 90–91 ºC; ν_{max} (KBr disc)/ cm^{-1} 3299 (N-H), 3271 (N-H), 3125 (Ar-H), 3033 (Ar-H), 2986 (C-H), 2953 (C-H), 1737 (C=O), 1709 (C=O), 1646 (N-H bend) and 1578 (Ar C=C); δ_N ($(CD_3)_2S(O)$) 138 (*N*HC(O)), 96.5 (N_{Pro}C(O)O), 65.9 (*N*HCHCF$_3$); δ_F (376 MHz, CD_3OD, rotamers A:B 1.1:1) –76.86 (B, 3F, d, *J* 7.7, CF_3) and –76.89 (A, 3F, d, *J* 7.7, CF_3); δ_H (300 MHz, CD_3OD, rotamers A:B 1.1:1) 7.37–7.28 (A, 5H, m, Ar*H* & B, 5H, m, Ar*H*), 5.11 (B, 2H, br s, PhCH_2), 5.09 (A, 2H, br s, PhCH_2), 4.25–4.21 (A, 1H, m, N_{Pro}C*H* & B, 1H, m, N_{Pro}C*H*), 3.93 (B, 1H, app sext, *J* 7.0, C*H*CF$_3$), 3.80–3.68 (A, 1H, m, C*H*CF$_3$), 3.72 (A, 3H, s, OCH_3 & B, 3H, s, OCH_3), 3.62–3.45 (A, 2H, m, N_{Pro}CH_2 & B, 2H, m, N_{Pro}CH_2), 2.69 (B, 2H, d, *J* 6.2, C(O)CH_2), 2.61 (A, 2H, d, *J* 6.5, C(O)CH_2), 2.31–2.13 (A, 1H, m, N_{Pro}CHCH_AH$_B$ & B, 1H, m, N_{Pro}CHCH_AH$_B$) and 2.04–1.86 (A, 3H, m, N_{Pro}CHCH$_A$$H_BCH_2$ & B, 3H, m, N_{Pro}CHCH$_A$$H_BCH_2$); δ_C (75 MHz, CD_3OD) 174.8 (*C*(O)NH), 174.7 (*C*(O)NH), 171.8 (*C*(O)OCH$_3$), 171.6 (*C*(O)OCH$_3$), 156.3 (N_{Pro}*C*(O)O), 138.0 (*C*Ar$_{ipso}$), 137.9 (*C*Ar$_{ipso}$), 129.5 (*C*Ar), 129.1 (*C*Ar), 128.9 (*C*Ar), 128.8 (*C*Ar), 123.6 (q, *J* 218, *C*F$_3$), 68.3 (*C*H$_2$Ph), 60.5 (N_{Pro}*C*H), 60.0 (N_{Pro}*C*H), 59.6 (q, *J* 28.1, *C*HCF$_3$), 59.4 (q, *J* 28.3, *C*HCF$_3$), 52.7 (O*C*H$_3$), 48.0 (N_{Pro}*C*H$_2$), 32.9 (C(O)*C*H$_2$), 32.5 (N_{Pro}CH*C*H$_2$), 31.4 (N_{Pro}CH*C*H$_2$) 25.4 (N_{Pro}CHCH$_2$*C*H$_2$) and 24.6 (N_{Pro}CHCH$_2$*C*H$_2$); ***m/z*** HRMS (ESI^+) $C_{18}H_{23}N_3O_5F_3$ ($[M+H]^+$) requires 418.1584, found 418.1586 (+0.4 ppm).

2-(1,1,1-Trifluoro-4-methoxy-4-oxobutan-2-yl)hydrazin-1-ium trifluoromethanesulfonate 172



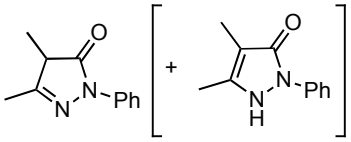
172

To a solution of crude (*RS*)-5-(trifluoromethyl)pyrazolidin-3-one **84** (90.0 mg, 0.570 mmol) in methanol (1 mL) was added triflic acid (101 μL, 1.14 mmol) and the mixture stirred at rt overnight. The resulting solution was then concentrated *in vacuo* for 4 h to remove excess triflic acid to give the title compound as a colourless solid (175 mg, 91 %).

ν_{max} (film)/ cm^{-1} 3300 (N-H), 3144 (N-H), 2990 (C-H), 2968 (C-H) and 1717 (C=O); ***mp*** 73–77 ºC; δ_F (375 MHz, CD_3OD) –77.3 (3F, d, *J* 7.7, CHCF_3) and –80.7 (3F, s, SO$_3$CF_3); δ_H (400 MHz, CD_3OD) 4.06 (1H, dqd, *J* 10.1, 6.9, 3.5, C*H*CF$_3$), 3.77 (3H, s, OCH_3), 2.91 (1H, dd, ABX system, J_{AB} 17.5, J_{AX} 3.5, C(O)H_AH$_B$) and 2.69 (1H, dd, ABX system, J_{BA} 17.5, J_{BX} 10.1, C(O)H$_A$$H_B$); δ_C (75 MHz, CD_3OD) 172.0 (*C*(O)OCH$_3$), 126.4 (q, *J* 281, *C*F$_3$), 121.8 (q, *J* 320,

SO_3CF_3), 58.2 (q, *J* 30.1, *C*HCF_3), 53.0 (O*C*H_3) and 33.2 (C(O)*C*H_2); ***m/z*** HRMS (ESI^+) $C_5H_{10}F_3N_2O_2$ ($[M–OTf]^+$) requires 187.0689, found 187.0686 (-1.5 ppm).

4,5-Dimethyl-2-phenyl-5-pyrazolin-3-one 198 (and 4,5-dimethyl-2-phenyl-4-pyrazolin-3-one 198´)

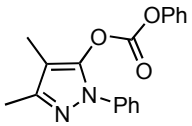


198 **198'**

Ethyl 2-methylacetoacetate **197** (4.00 mL, 28.3 mmol) and phenylhydrazine (3.00 mL, 31.1 mmol) were combined according to general procedure G. The resultant yellow oil was solidified upon trituration in petrol and a small volume of diethyl ether to give the title compound as an off-white solid, with spectroscopic data in accordance with the literature (4.95 g, 93 %).[152]

mp 122–127 ˚C; ***δ$_H$*** (300 MHz, $CDCl_3$, 5:1 **198**:**198´**) 7.91–7.86 (**198**, 2H, m, Ar*H*), 7.71–7.69 (**198´**, 2H, m, Ar*H*), 7.43–7.34 (**198**, 2H, m, Ar*H* & **198´**, 2H, m, Ar*H*), 7.21–7.13 (**198**, 1H, m, Ar*H* & **198´**, 1H, m, Ar*H*), 3.24 (**198**, 1H, q, *J* 7.9, C*H*), 2.16 (**198**, 3H, s, C(5)CH_3 & **198´**, 3H, s, C(5)CH_3), 1.83 (**198´**, 3H, s, C(4)CH_3) and 1.44 (**198**, 3H, d, *J* 7.9, C(4)CH_3).

4,5-Dimethyl-2-phenyl-2*H*-pyrazol-3-yl phenyl carbonate 199

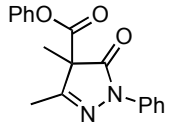


199

4,5-Dimethyl-2-phenyl-5-pyrazolin-3-one **198** (1.00 g, 5.31 mmol), triethylamine (0.810 mL, 5.84 mmol) and phenyl chloroformate (0.790 mL, 5.58 mmol) were combined according to general procedure H to give the title compound as a colourless solid (1.60 g, 97 %).

ν_{max} (KBr disc)/ cm^{-1} 3061 (Ar-H), 2944 (C-H), 2918 (C-H), 1787 (C=O), 1620 (C=N) and 1595 (C=C); ***mp*** 57–59 ˚C; ***δ$_H$*** (300 MHz, $CDCl_3$) 7.60–7.56 (2H, m, Ar*H*), 7.50–7.44 (2H, m, Ar*H*), 7.40–7.33 (2H, m, Ar*H*), 7.31–7.23 (2H, m, Ar*H*), 7.17–7.10 (2H, m, Ar*H*), 2.28 (3H, s, C(5)CH_3) and 2.00 (3H, s, C(4)CH_3); ***δ$_C$*** (75 MHz, $CDCl_3$) 150.8 (O*C*Ar$_{ipso}$), 149.9 (*C*(O)O), 148.5 (*C*(5)CH_3), 141.6 (*C*(3)O), 138.1 (N*C*Ar$_{ipso}$), 129.8 (*C*Ar), 129.4 (*C*Ar), 127.2 (*C*Ar), 126.8 (*C*Ar), 122.6 (*C*Ar), 120.6 (*C*Ar), 104.3 (*C*(4)CH_3), 12.9 (C(5)*C*H_3) and 7.14 (C(4)*C*H_3); ***m/z*** HRMS (ESI^+) $C_{18}H_{17}N_2O_3$ ($[M+H]^+$) requires 309.1234, found 309.1229 (–1.5 ppm).

(*RS*)-Phenyl (4,5-dimethyl-2-phenyl-5-pyrazolin-3-one)-4-carboxylate 200

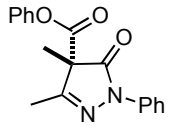


200

4,5-Dimethyl-2-phenyl-2*H*-pyrazol-3-yl phenyl carbonate **199** (31.0 mg, 0.100 mmol), triazolium salt **176** (5.50 mg, 20.0 μmol) and KHMDS (0.5 M solution in toluene, 36.0 μL, 18.0 μmol) were combined according to general procedure J. The crude material was purified by column chromatography on silica gel, eluting with 15 % diethyl ether in petrol to give the title compound as a colourless oil (20 mg, 65 %).

ν_{max} (KBr disc)/ cm^{-1} 3065 (Ar-H), 2988 (C-H), 2936 (C-H), 1764 (C=O), 1713 (C=O), 1621 (Ar C=C) and 1596 (C=N); δ_H (300 MHz, $CDCl_3$) 7.96–7.93 (2H, m, Ar*H*), 7.45–7.35 (4H, m, Ar*H*), 7.27–7.19 (2H, m, Ar*H*), 7.09–7.05 (2H, m, Ar*H*), 2.26 (3H, s, C(5)CH_3) and 1.73 (3H, s, C(4)CH_3); δ_C (75 MHz, $CDCl_3$) 170.4 (*C*(3)O), 164.9 (*C*(O)O), 158.3 (*C*(5)CH_3), 150.3 (O*C*Ar$_{ipso}$), 137.8 (N*C*Ar$_{ipso}$), 129.7 (*C*Ar), 129.1 (*C*Ar), 126.7 (*C*Ar), 125.6 (*C*Ar), 121.2 (*C*Ar), 119.0 (*C*Ar), 61.6 (*C*(4)CH_3), 17.3 (C(4)*C*H_3) and 14.4 (C(5)*C*H_3); ***m/z*** HRMS (ESI^+) $C_{18}H_{17}N_2O_3$ ($[M+H]^+$) requires 309.1234, found 309.1233 (–0.2 ppm).

(–)-Phenyl (4,5-dimethyl-2-phenyl-5-pyrazolin-3-one)-4-carboxylate (–)-200



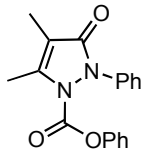
(–)-200

4,5-Dimethyl-2-phenyl-2*H*-pyrazol-3-yl phenyl carbonate **199** (31.0 mg, 0.100 mmol), triazolium salt **185** (3.50 mg, 10.0 μmol) and KHMDS (18.0 μL, 0.5 M solution in toluene, 9.00 μmol) were combined according to general procedure K. The crude material was purified by column chromatography on silica gel, eluting with 15 % diethyl ether in petrol to give the title compound as a colourless oil with an enantiomeric excess of 46 % (23 mg, 74 %).

Enantiomeric excess was determined by HPLC with ChiralPax AS-H column (1 % isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 254 nm), t_R(+) 13.3 min and t_R(–) 14.7 min. When reaction was carried out with triazolium salt **217**, an enantiomeric excess of 62 % was obtained in 61 % yield.

$[\alpha]^{20}_D$ –108 (*c* 0.3, chloroform).

Phenyl (4,5-dimethyl-2-phenyl-4-pyrazolin-3-one)-1-carboxylate 201

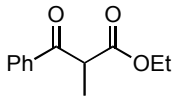


201

4,5-Dimethyl-2-phenyl-2*H*-pyrazol-3-yl phenyl carbonate **199** (200 mg, 0.650 mmol) and DMAP (15.9 mg, 0.130 mmol) were combined according to general procedure I. The crude material was purified by column chromatography on silica gel, eluting with 50 % diethyl ether in petrol to give the title compound as a colourless solid (112 mg, 56 %).

$\boldsymbol{\nu}_{\mathbf{max}}$ (KBr disc)/ cm^{-1} 3074 (Ar-H), 3045 (Ar-H), 2924 (C-H), 1753 (C=O), 1686 (C=O), 1649 and 1589 (C=C); ***mp*** 140–141 ˚C; $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.47–7.40 (4H, m, Ar*H*), 7.32–7.26 (3H, m, Ar*H*), 7.19 (1H, tt, *J* 7.4, 1.2, Ar*H*), 6.83–6.79 (2H, m, Ar*H*), 2.58 (3H, d, *J* 0.8, C(5)CH_3) and 1.93 (3H, d, *J* 0.8, C(4)CH_3); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 167.9 (*C*(3)O), 149.9 (*C*(5)CH_3), 149.4 (O*C*Ar_{ipso}), 148.6 (*C*(O)O), 139.2 (N*C*Ar_{ipso}), 129.6 (*C*Ar), 129.1 (*C*Ar), 126.8 (*C*Ar), 126.6 (*C*Ar), 123.2 (*C*Ar), 120.9 (*C*Ar), 111.0 (*C*(4)CH_3), 13.9 (C(5)*C*H_3) and 7.3 (C(4)*C*H_3); ***m/z*** HRMS (ESI^+) $C_{18}H_{17}N_2O_3$ ($[M+H]^+$) requires 309.1234, found 309.1235 (+0.4 ppm).

Ethyl 2-methyl-3-oxo-3-phenylpropanoate 202

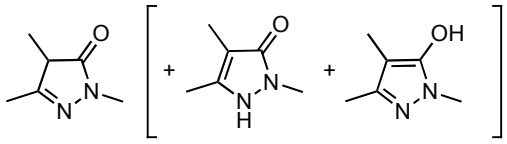


202

Based upon a procedure by Hii and co-workers,[133] (ethyl 3-oxo-3-phenylpropanoate **63** (10.0 mL, 58.0 mmol), potassium carbonate (12.0 g, 87.0 mmol) and iodomethane (5.40 mL, 87.0 mmol) were combined in acetonitrile (200 mL) and refluxed for 3 days. Reaction was diluted with water (300 mL) and extracted with diethyl ether (2 x 250 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel, eluting with 5 % ethyl acetate in petrol to give the title compound as a colourless oil, with spectroscopic data in accordance with the literature (5.14 g, 42 %).[133]

$\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 8.00–7.96 (2H, m, Ar*H*), 7.61–7.56 (1H, m, Ar*H*), 7.51–7.45 (2H, m, Ar*H*), 4.37 (1H, q, *J* 7.0, C*H*), 4.15 (2H, q, *J* 7.1, OCH_2), 1.50 (3H, d, *J* 7.0, CHCH_3) and 1.17 (3H, t, *J* 7.1, OCH_2CH_3).

2,4,5-Trimethyl-5-pyrazolin-3-one 203 (and 2,4,5-trimethyl-4-pyrazolin-3-one 203′ and 2,4,5-trimethyl-2*H*-pyrazol-3-one 203″)

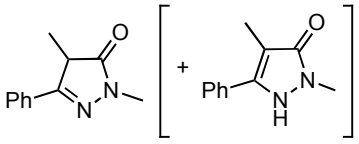


203 **203'** **203''**

Ethyl 2-methylacetoacetate **197** (2.00 mL, 14.2 mmol) and methylhydrazine (0.820 mL, 15.6 mmol) were combined according to general procedure G. The resultant yellow oil was solidified upon trituration in diethyl ether to give the title compound as a colourless solid (1.52 g, 85 %).

ν_{max} (KBr disc)/ cm^{-1} (**203″** only) 3150–2000 (O-H), 2917 (C-H), 2723 (C-H), 2576 (C-H), 1614 (C=N) and 1587 (C=C); ***mp*** 128–131 ˚C; δ_H (300 MHz, $CDCl_3$, 1.1:1 **203**:**203′**) 3.34 (**203′**, 3H, s, NCH_3), 3.26 (**203**, 3H, s, NCH_3), 2.97 (**203**, 1H, q, *J* 8.0, C*H*), 2.07 (**203′**, 3H, s, C(5)CH_3), 2.04 (**203**, 3H, s, C(5)CH_3), 1.75 (**203′**, 3H, s, C(4)CH_3) and 1.32 (**203**, 3H, d, *J* 8.0, CHCH_3); δ_C (75 MHz, $CDCl_3$) 175.7 (**203**, *C*(O)), 163.1 (**203′**, *C*(O)), 160.4 (**203**, *C*CH_3), 144.1 (**203′**, *C*(5)CH_3), 100.0 (**203′**, *C*(4)CH_3), 45.8 (**203**, *C*H), 31.2 (**203**, N*C*H_3), 31.0 (**203′**, N*C*H_3), 15.3 (**203**, C*C*H_3), 12.1 (**203**, CH*C*H_3), 11.1 (**203′**, C(5)*C*H_3) and 6.8 (**203′**, C(4)*C*H_3); ***m/z*** HRMS (ESI^+) $C_6H_{10}N_2O$ ($[M]^+$) requires 126.0788, found 126.0787 (–0.5 ppm).

2,4-Dimethyl-5-phenyl-5-pyrazolin-3-one 204 (and 2,4-dimethyl-5-phenyl-4-pyrazolin-3-one 204′)

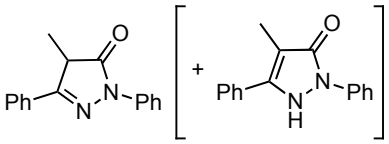


204 **204'**

Ethyl 2-methyl-3-oxo-3-phenylpropanoate **202** (2.00 g, 9.70 mmol) and methylhydrazine (0.560 mL, 10.7 mmol) were combined according to general procedure G. The resultant yellow oil was solidified upon trituration in a mixture of petrol, diethyl ether and a small volume of dichloromethane to give the title compound as a colourless solid, with spectroscopic data in accordance with the literature (1.17 g, 64 %).[130]

mp 101–105 ˚C; δ_H (300 MHz, $CDCl_3$, 9:1 **204**:**204′**) 7.68–7.65 (**204**, 2H, m, Ar*H*), 7.57–7.54 (**204′**, 1H, m, Ar*H*), 7.50–7.47 (**204′**, 2H, m, Ar*H*), 7.48–7.41 (**204**, 3H, m, Ar*H*), 7.34–7.31 (**204′**, 2H, m, Ar*H*), 3.61 (**204′**, 3H, s, NCH_3), 3.63 (**204**, 1H, q, *J* 7.9, C*H*CH_3), 3.41 (**204**, 3H, s, NCH_3), 1.92 (**204′**, 3H, s, CCH_3) and 1.48 (**204**, 3H, s, CHCH_3).

4-Methyl-2,5-diphenyl-5-pyrazolin-3-one 205 (and 4-methyl-2,5-diphenyl-4-pyrazolin-3-one 205′)

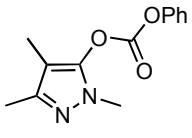


205 **205'**

Ethyl 2-methyl-3-oxo-3-phenylpropanoate **202** (2.00 g, 9.70 mmol) and phenylhydrazine (1.05 mL, 10.7 mmol) were combined according to general procedure G. The resultant brown oil was taken up in toluene (10 mL) and subjected to a further reflux overnight before being concentrated *in vacuo*. The resultant oil solidified upon trituration in diethyl ether to give the title compound as a light brown solid (1.48 g, 81 %).

ν_{max} (KBr disc)/ cm^{-1} (**205** only) 3063 (Ar-H), 2982 (C-H), 2938 (C-H), 1711 (C=O) and 1598 (C=N); ***mp*** 112–114 ˚C; δ_H (300 MHz, $CDCl_3$, 11:1 **205**:**205′**) 8.03–8.00 (**205**, 2H, m, Ar*H*), 7.84–7.81 (**205′**, 2H, m, Ar*H*), 7.80–7.75 (**205**, 2H, m, Ar*H*), 7.67–7.63 (**205′**, 2H, m, Ar*H*), 7.51–7.39 (**205**, 5H, m, Ar*H* & **205′**, 1H, m, Ar*H*), 7.25–7.18 (**205**, 1H, m, Ar*H*), 3.80 (**205**, 1H, q, *J* 7.9, C*H*), 2.09 (**205′**, 3H, s, CH_3) and 1.59 (**205**, 3H, d, *J* 7.9, CH_3); δ_C (125 MHz, $CDCl_3$) 174.4 (**205**, *C*(O)), 164.0 (**205′**, *C*(O)), 159.7 (**205**, *C*Ph), 149.3 (**205′**, *C*Ph), 138.3 (**205**, NCAr_{ipso}), 130.7 (**205**, *C*Ar), 130.6 (**205**, CCAr_{ipso}), 129.7 (**205′**, *C*Ar), 129.1 (**205**, *C*Ar), 129.0 (**205**, *C*Ar), 127.5 (**205′**, *C*Ar), 126.7 (**205**, *C*Ar), 125.3 (**205**, *C*Ar), 119.5 (**205′**, *C*Ar), 119.1 (**205**, *C*Ar), 107.5 (**205′**, *C*(4)), 44.7 (**205**, *C*H), 15.1 (**205**, *C*H_3) and 8.1 (**205′**, *C*H_3); ***m/z*** HRMS (ESI^+) $C_{16}H_{15}N_2O$ ($[M+H]^+$) requires 251.1179, found 251.1181 (+0.8 ppm).

2,4,5-Trimethyl-2*H*-pyrazol-3-yl phenyl carbonate 206



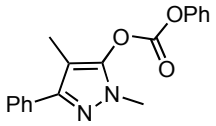
206

2,4,5-Trimethyl-5-pyrazolin-3-one **203** (500 mg, 3.96 mmol), triethylamine (0.600 mL, 4.33 mmol) and phenyl chloroformate (0.520 mL, 4.15 mmol) were combined according to general procedure H. The crude material was purified by column chromatography on silica gel, eluting with 50 % diethyl ether in petrol to give the title compound as a colourless solid (571 mg, 59 %).

ν_{max} (KBr disc)/ cm^{-1} 2948 (C-H), 2925 (C-H), 1793 (C=O), 1607 (C=N) and 1593 (C=C);

mp 38–40 ˚C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.38–7.35 (2H, m, Ar*H*), 7.25–7.19 (3H, m, Ar*H*), 3.62 (3H, s, NCH_3), 2.10 (3H, s, C(5)CH_3) and 1.84 (3H, s, C(4)CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 150.9 (O*C*Ar$_{ipso}$), 150.1 (*C*(O)O), 146.4 (*C*(5)CH_3), 142.2 (*C*(3)O), 129.9 (*C*Ar), 126.9 (*C*Ar), 120.6 (*C*Ar), 101.9 (*C*(4)CH_3), 34.6 (N*C*H_3), 12.7 (C(5)*C*H_3) and 7.15 (C(4)*C*H_3); ***m/z*** HRMS (ESI^+) $C_{13}H_{15}N_2O_3$ ($[M+H]^+$) requires 247.1077, found 247.1080 (+1.1 ppm).

2,4-Dimethyl-5-phenyl-2*H*-pyrazol-3-yl phenyl carbonate 207

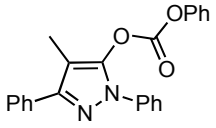


207

2,4-Dimethyl-5-phenyl-5-pyrazolin-3-one **204** (500 mg, 2.67 mmol), triethylamine (0.400 mL, 2.89 mmol) and phenyl chloroformate (0.350 mL, 2.80 mmol) were combined according to general procedure H. The crude material was purified by column chromatography on silica gel, eluting with 25 % diethyl ether in petrol to give the title compound as a colourless solid (740 mg, 90 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3094 (Ar-H), 3066 (Ar-H), 2945 (C-H), 2875 (C-H), 1783 (C=O), 1600 (C=N) and 1572 (C=C); ***mp*** 57–58 ˚C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.67–7.66 (2H, m, Ar*H*), 7.47–7.41 (4H, m, Ar*H*), 7.35–7.30 (4H, m, Ar*H*), 3.83 (3H, s, NCH_3) and 2.16 (3H, s, CCH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 150.9 (O*C*Ar$_{ipso}$), 150.2 (*C*(O)O), 148.8 (*C*Ph), 142.9 (*C*(3)O), 134.0 (C*C*Ar$_{ipso}$), 129.9 (*C*Ar), 128.6 (*C*Ar), 127.7 (*C*Ar), 127.4 (*C*Ar), 126.9 (*C*Ar), 120.6 (*C*Ar), 102.0 (*C*CH_3), 35.1 (N*C*H_3) and 8.59 (C*C*H_3); ***m/z*** HRMS (ESI^+) $C_{18}H_{17}N_2O_3$ ($[M+H]^+$) requires 309.1234, found 309.1237 (+1.1 ppm).

4-Methyl-2,5-diphenyl-2*H*-pyrazol-3-yl phenyl carbonate 208



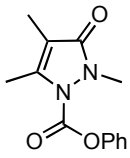
208

4-Methyl-2,5-diphenyl-5-pyrazolin-3-one **205** (668 mg, 2.67 mmol), triethylamine (0.400 mL, 2.89 mmol) and phenyl chloroformate (0.350 mL, 2.80 mmol) were combined according to general procedure H to give the title compound as a colourless solid (880 mg, 89 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3063 (Ar-H), 2959 (C-H), 2921 (C-H), 1779 (C=O), 1604 (C=N) and 1575 (C=C); ***mp*** 75–78 ˚C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.77 (2H, d, *J* 7.2, Ar*H*), 7.69 (2H, d, *J* 7.9,

Ar*H*), 7.51 (2H, t, *J* 7.9, Ar*H*), 7.46 (2H, t, *J* 7.7, Ar*H*), 7.40–7.37 (4H, m, Ar*H*), 7.28 (1H, dd, *J* 7.1, 3.1, Ar*H*), 7.10 (2H, d, *J* 7.7, Ar*H*) and 2.25 (3H, s, CCH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 150.8 (OCAr_{ipso}), 150.3 (*C*Ph), 149.9 (*C*(O)O), 142.3 (*C*(3)O), 138.1 (NCAr_{ipso}), 133.7 (CCAr_{ipso}), 129.8 (*C*Ar), 129.5 (*C*Ar), 128.6 (*C*Ar), 128.1 (*C*Ar), 127.7 (*C*Ar), 127.6 (*C*Ar), 126.9 (*C*Ar), 122.9 (*C*Ar), 120.6 (*C*Ar), 104.2 (*C*CH_3) and 8.62 (C*C*H_3); ***m/z*** HRMS (ESI^+) $C_{23}H_{19}N_2O_3$ ($[M+H]^+$) requires 371.1390, found 371.1391 (+0.2 ppm).

Phenyl (2,4,5-trimethyl-4-pyrazolin-3-one)-1-carboxylate 209

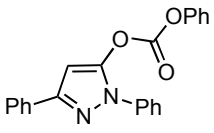


209

2,4,5-Trimethyl-2*H*-pyrazol-3-yl phenyl carbonate **211** (24.6 mg, 0.100 mmol) and DMAP (2.40 mg, 20.0 μmol) were combined according to general procedure I. The crude material was purified by trituration in diethyl ether give the title compound as a colourless solid (19 mg, 77 %).

$\boldsymbol{\nu_{max}}$ (KBr disc)/ cm^{-1} 3068 (Ar-H), 2927 (C-H), 1748 (C=O), 1677 (C=O), 1646 and 1590 (C=C); ***mp*** 90–91 ˚C; $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.44 (2H, app t, *J* 7.8, *m*-Ar*H*), 7.31 (1H, t, *J* 7.5, *p*-Ar*H*), 7.20 (2H, d, *J* 8.0, *o*-Ar*H*), 3.55 (3H, s, NCH_3), 2.46 (3H, s, C(5)CH_3) and 1.88 (3H, s, C(4)CH_3); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 169.3 (*C*(3)O), 149.9 (OCAr_{ipso}), 148.5 (*C*(O)O), 147.4 (*C*(5)CH_3), 129.9 (*C*Ar), 126.9 (*C*Ar), 121.3 (*C*Ar), 111.5 (*C*(4)CH_3), 35.1 (N*C*H_3), 14.1 (C(5)*C*H_3) and 7.3 (C(4)*C*H_3); ***m/z*** HRMS (ESI^+) $C_{13}H_{15}N_2O_3$ ($[M+H]^+$) requires 247.1077, found 247.1080 (+0.4 ppm).

2,5-Diphenyl-2*H*-pyrazol-3-yl phenyl carbonate 210

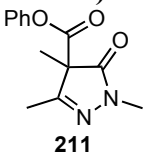


210

2,5-Diphenyl-5-pyrazolin-3-one **65** (200 mg, 0.850 mmol), triethylamine (0.130 mL, 0.930 mmol) and phenyl chloroformate (0.110 mL, 0.89 mmol) were combined according to general procedure H. The crude material was purified by column chromatography on silica gel, eluting with a gradient of 10 % diethyl ether in petrol to give the title compound as a brown solid (170 mg, 56 %).

ν_{max} (KBr disc)/ cm^{-1} 3057 (Ar-H), 1784 (C=O) and 1593 (C=N); ***mp*** 79–80 ˚C; δ_H (300 MHz, $CDCl_3$) 7.90–7.87 (2H, m, Ar*H*), 7.75–7.72 (2H, m, Ar*H*), 7.55–7.50 (2H, m, Ar*H*), 7.46–7.30 (7H, m, Ar*H*), 7.19–7.16 (2H, m, Ar*H*) and 6.75 (1H, s, C(4)*H*); δ_C (75 MHz, $CDCl_3$) 151.0 (*C*(5)Ph), 150.7 (O*C*Ar_{ipso}), 149.2 (*C*(O)O), 145.0 (*C*(3)O), 137.9 (N*C*Ar_{ipso}), 132.9 (C*C*Ar_{ipso}), 129.8 (*C*Ar), 129.4 (*C*Ar), 128.7 (*C*Ar), 128.4 (*C*Ar), 127.7 (*C*Ar), 126.9 (*C*Ar), 125.6 (*C*Ar), 123.3 (*C*Ar), 120.7 (*C*Ar) and 93.0 (*C*(4)H); ***m/z*** HRMS (ESI^+) $C_{22}H_{17}N_2O_3$ ($[M+H]^+$) requires 357.1234, found 357.1229 (–1.3 ppm).

(*RS*)-Phenyl (2,4,5-trimethyl-5-pyrazolin-3-one)-4-carboxylate 211

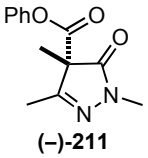


211

2,4,5-Trimethyl-2*H*-pyrazol-3-yl phenyl carbonate **206** (24.6 mg, 0.100 mmol), triazolium salt **175** (5.50 mg, 20.0 μmol) and KHMDS (0.5 M solution in toluene, 36.0 μL, 18.0 μmol) were combined according to general procedure J. The crude material was purified by column chromatography on silica gel, eluting with 25 % diethyl ether in petrol to give the title compound as a colourless solid (11 mg, 45 %).

ν_{max} (KBr disc)/ cm^{-1} 3059 (Ar-H), 2985 (C-H), 2941 (C-H), 1762 (C=O), 1708 (C=O), 1607 (Ar C=C) and 1592 (C=N); ***mp*** 80–82 ˚C; δ_H (300 MHz, $CDCl_3$) 7.40–7.34 (2H, m, Ar*H*), 7.24 (1H, tt, *J* 7.4, 1.2, Ar*H*), 7.07–7.03 (2H, m, Ar*H*), 3.36 (3H, s, NCH_3), 2.14 (3H, s, C(5)CH_3) and 1.61 (3H, s, C(4)CH_3); δ_C (75 MHz, $CDCl_3$) 172.1 (*C*(3)O), 165.2 (*C*(O)O), 157.6 (*C*(5)CH_3), 150.3 (*C*Ar_{ipso}), 129.7 (*C*Ar), 126.6 (*C*Ar), 121.3 (*C*Ar), 59.9 (*C*(4)CH_3), 31.6 (N*C*H_3), 19.9 (C(4)*C*H_3) and 14.2 (C(5)*C*H_3); ***m/z*** HRMS (ESI^+) $C_{13}H_{15}N_2O_3$ ($[M+H]^+$) requires 247.1077, found 247.1082 (+1.9 ppm).

(–)-Phenyl (2,4,5-trimethyl-5-pyrazolin-3-one)-4-carboxylate (–)-211



(–)-211

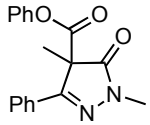
2,4,5-Trimethyl-2*H*-pyrazol-3-yl phenyl carbonate **206** (24.6 mg, 0.100 mmol), triazolium salt **217** (4.70 mg, 10.0 μmol) and KHMDS (0.5 M solution in toluene, 18.0 μL, 9.00 μmol) were combined according to general procedure K. The crude material was purified by column chromatography on silica gel, eluting with 40 % diethyl ether in petrol to give the title

compound as a colourless solid with an enantiomeric excess of 86 % (15 mg, 61 %).

$[\alpha]^{20}_D$ –116.9 (*c* 0.1, chloroform); ***mp*** 94–95 ˚C.

Enantiomeric excess was determined by HPLC with ChiralPax AS-H column (1 % isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 254 nm), t_R(+) 17.3 min and t_R(–) 24.0 min.

(*RS*)-Phenyl (2,4-dimethyl-5-phenyl-5-pyrazolin-3-one)-4-carboxylate 212

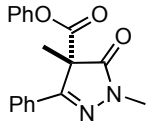


212

2,4-Dimethyl-5-phenyl-2*H*-pyrazol-3-yl phenyl carbonate **207** (31.0 mg, 0.100 mmol), triazolium salt **175** (5.50 mg, 20.0 μmol) and KHMDS (0.5 M solution in toluene, 36.0 μL, 18.0 μmol) were combined according to general procedure J. The crude material was purified by column chromatography on silica gel, eluting with 10 % diethyl ether in petrol to give the title compound as a colourless solid (17 mg, 55 %).

ν_{max} (KBr disc)/ cm^{-1} 2921 (C-H), 2852 (C-H), 1759 (C=O), 1710 (C=O) and 1596 (C=N); ***mp*** 92 ˚C; δ_H (300 MHz, $CDCl_3$) 7.78–7.75 (2H, m, Ar*H*), 7.45–7.44 (3H, m, Ar*H*), 7.34–7.18 (3H, m, Ar*H*), 6.94–6.90 (2H, m, Ar*H*), 3.51 (3H, s, NCH_3) and 1.79 (3H, s, CCH_3); δ_C (75 MHz, $CDCl_3$) 172.4 (*C*(3)O), 166.2 (*C*(O)O), 156.5 (*C*Ph), 150.3 (OCAr_{ipso}), 130.8 (*C*Ar), 129.8 (CCAr_{ipso}), 129.6 (*C*Ar), 129.3 (*C*Ar), 126.6 (*C*Ar), 126.0 (*C*Ar), 121.3 (*C*Ar), 58.4 (*C*CH_3), 32.0 (N*C*H_3) and 18.8 (C*C*H_3); ***m/z*** HRMS (ESI^+) $C_{18}H_{17}N_2O_3$ ($[M+H]^+$) requires 309.1234, found 309.1238 (+1.4 ppm).

(–)-Phenyl (2,4-dimethyl-5-phenyl-5-pyrazolin-3-one)-4-carboxylate (–)-212



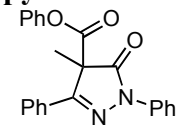
(–)-212

2,4-Dimethyl-5-phenyl-2*H*-pyrazol-3-yl phenyl carbonate **207** (31.0 mg, 0.100 mmol), triazolium salt **216** (3.80 mg, 10.0 μmol) and KHMDS (0.5 M solution in toluene, 18.0 μL, 9.00 μmol) were combined according to general procedure K. The crude material was purified by column chromatography on silica gel, eluting with 10 % diethyl ether in petrol to give the title compound as a colourless solid with an enantiomeric excess of 10 % (3.2 mg, 10 %).

Enantiomeric excess was determined by HPLC with ChiralPax AS-H column (1 % isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 211 nm), t_R(+) 15.1 min and t_R(–) 19.2 min.

$[\alpha]^{20}_D$ –1.0 (*c* 0.1, chloroform); ***mp*** 87–89 ºC.

(*RS*)-Phenyl (4-methyl-2,5-diphenyl-5-pyrazolin-3-one)-4-carboxylate 213

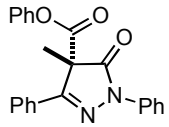


213

4-Methyl-2,5-diphenyl-2*H*-pyrazol-3-yl phenyl carbonate **208** (37.0 mg, 0.100 mmol), and DMAP (2.40 mg, 20.0 μmol) were combined according to general procedure J. The crude material was purified by column chromatography on silica gel, eluting with 10 % then 20 % diethyl ether in petrol to give the title compound as a colourless oil (9 mg, 24 %).

ν_{max} (KBr disc)/ cm^{-1} 3064 (Ar-H), 2931 (C-H), 2857 (C-H), 1764 (C=O), 1715 (C=O) and 1594 (C=N); δ_H (300 MHz, C_6D_6) 8.37–8.32 (2H, m, Ar*H*), 7.92–7.88 (2H, m, Ar*H*), 7.25–7.19 (2H, m, Ar*H*), 7.09–7.05 (3H, m, Ar*H*), 6.98 (1H, tt, *J*, 7.4, 1.3, Ar*H*), 6.82–6.70 (5H, m, Ar*H*), and 1.69 (3H, s, CH_3); δ_C (75 MHz, C_6D_6) 171.0 (*C*(3)O), 166.2 (*C*(O)O), 156.9 (*C*Ph), 150.8 (O*C*Ar$_{ipso}$), 138.7 (N*C*Ar$_{ipso}$), 131.0 (*C*Ar), 130.2 (C*C*Ar$_{ipso}$), 129.6 (*C*Ar), 129.4 (*C*Ar), 129.3 (*C*Ar), 126.5 (*C*Ar), 126.4 (*C*Ar), 125.8 (*C*Ar), 121.5 (*C*Ar), 119.3 (*C*Ar), 60.4 (*C*CH_3) and 18.9 (C*C*H_3); ***m/z*** HRMS (ESI^+) $C_{23}H_{19}N_2O_3$ ($[M+H]^+$) requires 371.1390, found 371.1389 (–0.3 ppm).

(+)-Phenyl (4-methyl-2,5-diphenyl-5-pyrazolin-3-one)-4-carboxylate (+)-213



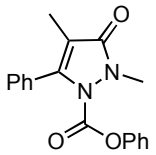
(+)-213

4-Methyl-2,5-diphenyl-2*H*-pyrazol-3-yl phenyl carbonate **208** (37.0 mg, 0.100 mmol), triazolium salt **217** (4.70 mg, 10.0 μmol) and KHMDS (0.5 M solution in toluene, 18.0 μL, 9.00 μmol) were combined according to general procedure K. The crude material was purified by column chromatography on silica gel, eluting with 10 % diethyl ether in petrol to give the title compound as a colourless oil with an enantiomeric excess of 20 % (18 mg, 48 %).

$[\alpha]^{20}_D$ +12.7 (*c* 0.9, chloroform).

Enantiomeric excess was determined by HPLC with ChiralPax IB column (1 % isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 254 nm), t_R(+) 9.86 min and t_R(–) 12.1 min.

Phenyl (2,4-dimethyl-5-phenyl-4-pyrazolin-3-one)-1-carboxylate 214



214

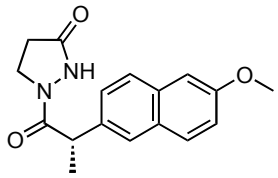
2,4-Dimethyl-5-phenyl-2*H*-pyrazol-3-yl phenyl carbonate **207** (31.0 mg, 0.100 mmol) and DMAP (2.40 mg, 20.0 μmol) were combined according to general procedure I. The crude material was purified by column chromatography on silica gel, eluting with 20 % diethyl ether in petrol then 50 % diethyl ether in petrol to give the title compound as a colourless solid (4.4 mg, 14 %) and residual starting material (10 mg, 32 %).

ν_{max} (KBr disc)/ cm^{-1} 3054 (Ar-H), 3020 (Ar-H), 2961 (C-H), 2921 (C-H), 1754 (C=O), 1680 (C=O), 1646 and 1597 (C=C); ***mp*** 83–85 ˚C; δ_H (300 MHz, $CDCl_3$) 7.44 (5H, app s, Ar*H*), 7.30–7.25 (2H, m, Ar*H*), 7.17 (1H, tt, *J* 6.4, 1.2, Ar*H*), 6.86–6.82 (2H, m, Ar*H*), 3.67 (3H, s, NCH_3) and 1.87 (3H, s, CCH_3); δ_C (75 MHz, $CDCl_3$) 168.4 (*C*(3)O), 149.8 (O*C*Ar_{ipso}), 149.7 (*C*Ph), 149.1 (*C*(O)O), 130.4 (C*C*Ar_{ipso}), 129.8 (*C*Ar), 129.6 (*C*Ar), 129.4 (*C*Ar), 128.4 (*C*Ar), 126.5 (*C*Ar), 120.7 (*C*Ar), 113.9 (*C*CH_3), 34.8 (N*C*H_3) and 8.0 (C*C*H_3); ***m/z*** HRMS (ESI^+) $C_{18}H_{17}N_2O_3$ ($[M+H]^+$) requires 309.1234, found 309.1236 (+0.7 ppm).

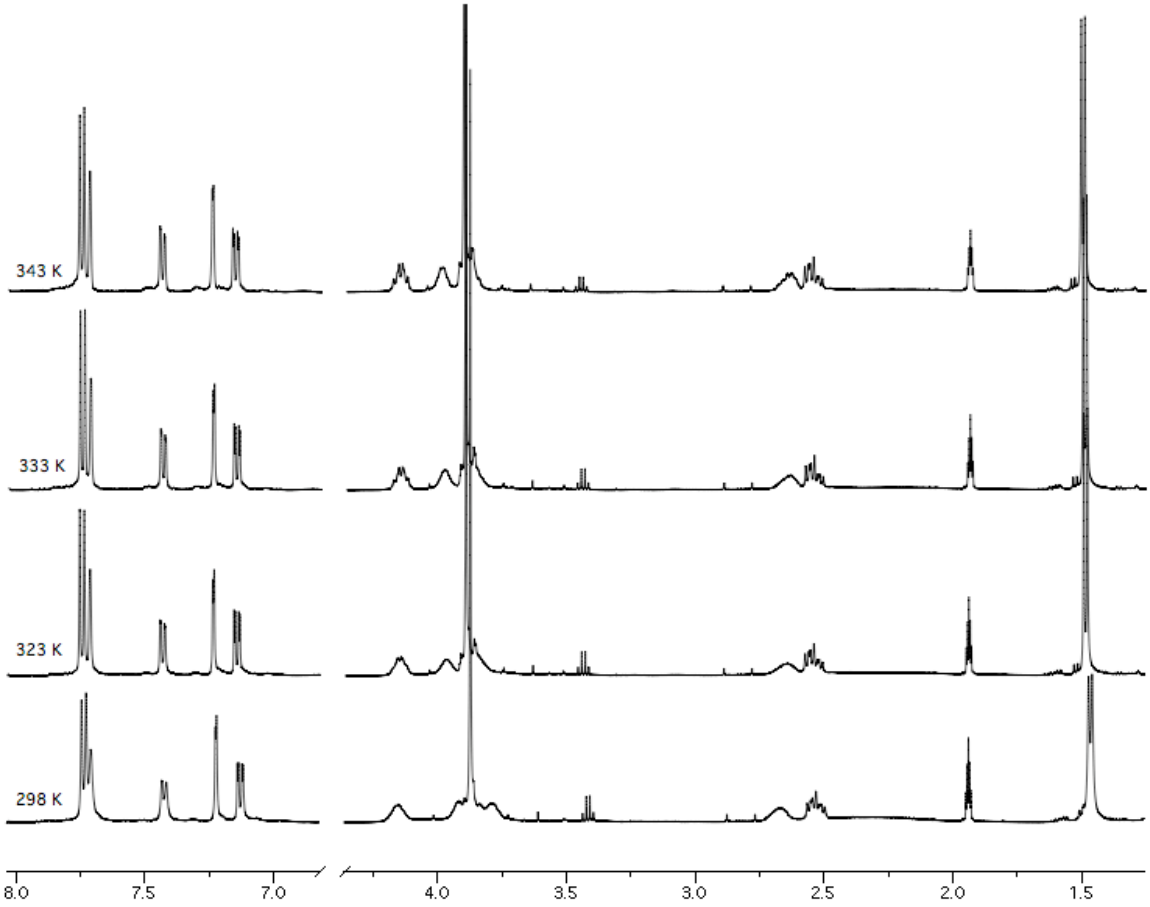
Appendix 1: Resolution of rotamers by variable temperature ^{1}H NMR spectroscopy

All reactions were carried out in a Bruker Avance 500 (500 MHz) spectrometer in the specified solvent.

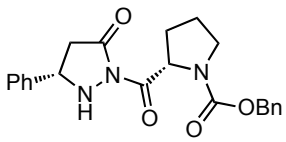
(*S*)-1-(2'-(6-Methoxynaphthalen-2-yl)propanoyl)pyrazolidin-3-one 149



149 (CD_3CN)

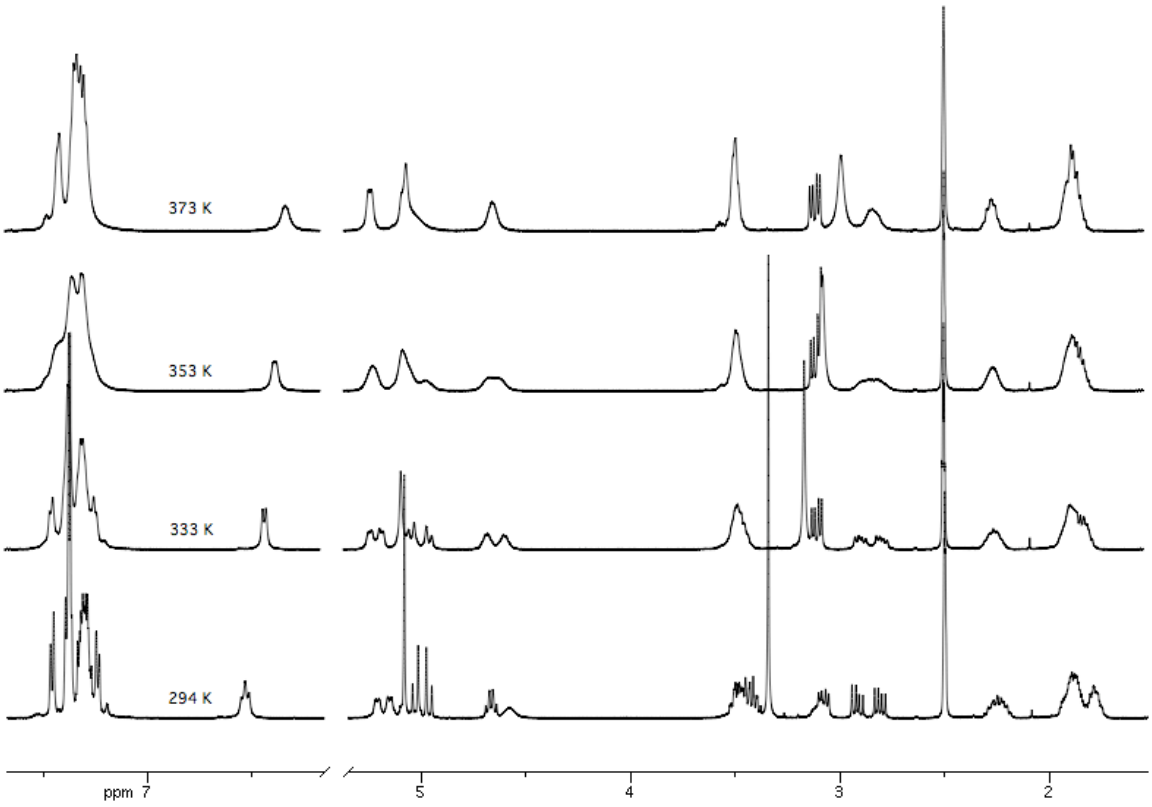


(*S*)-2-((*S*)-1'-((benzyloxy)carbonyl)pyrrolidine-2'-carbonyl)-5-phenylpyrazolidin-3-one (5*S*)-142

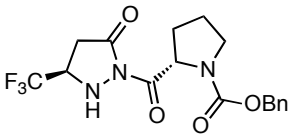


(5*S*)-142 $(CD_3)_2S(O)$)

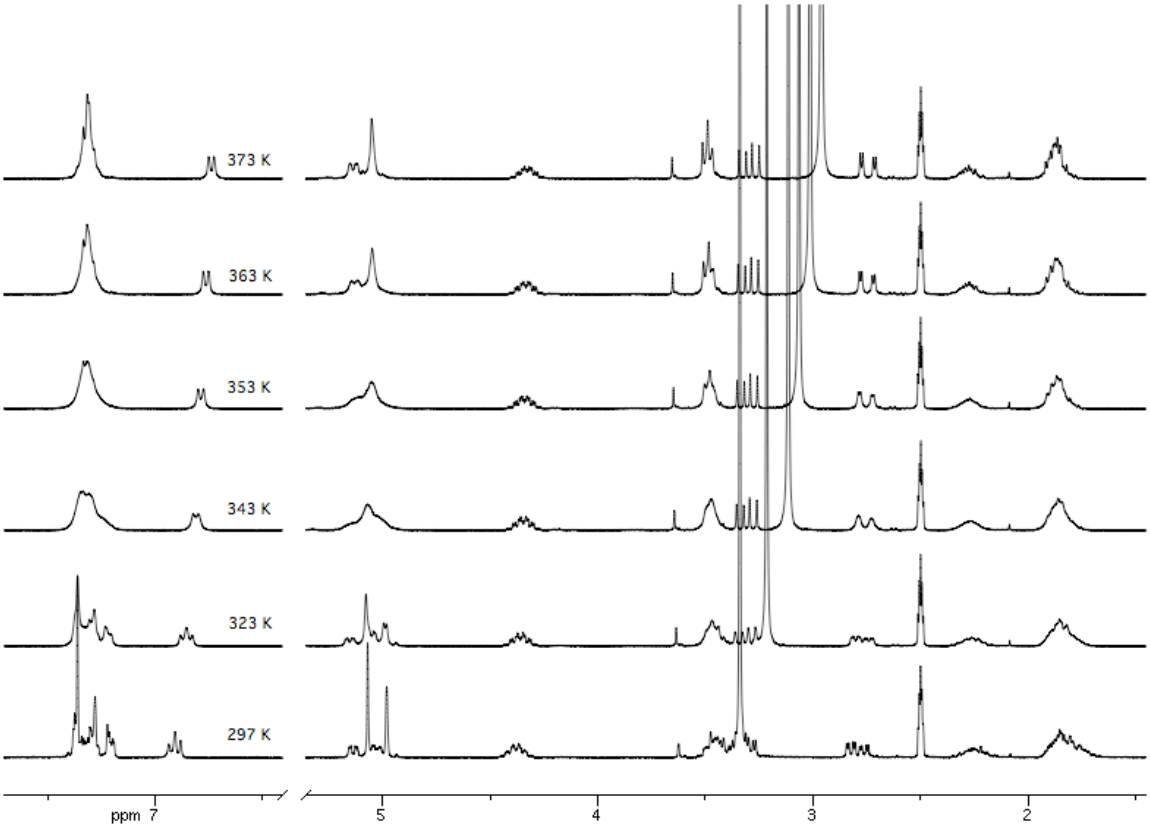
Consistent with, but not conclusive for, rotamers



(*R*)-2-((*S*)-1'-((benzyloxy)carbonyl)pyrrolidine-2'-carbonyl)-5-(trifluoromethyl)-pyrazolidin-3-one (5*R*)-163



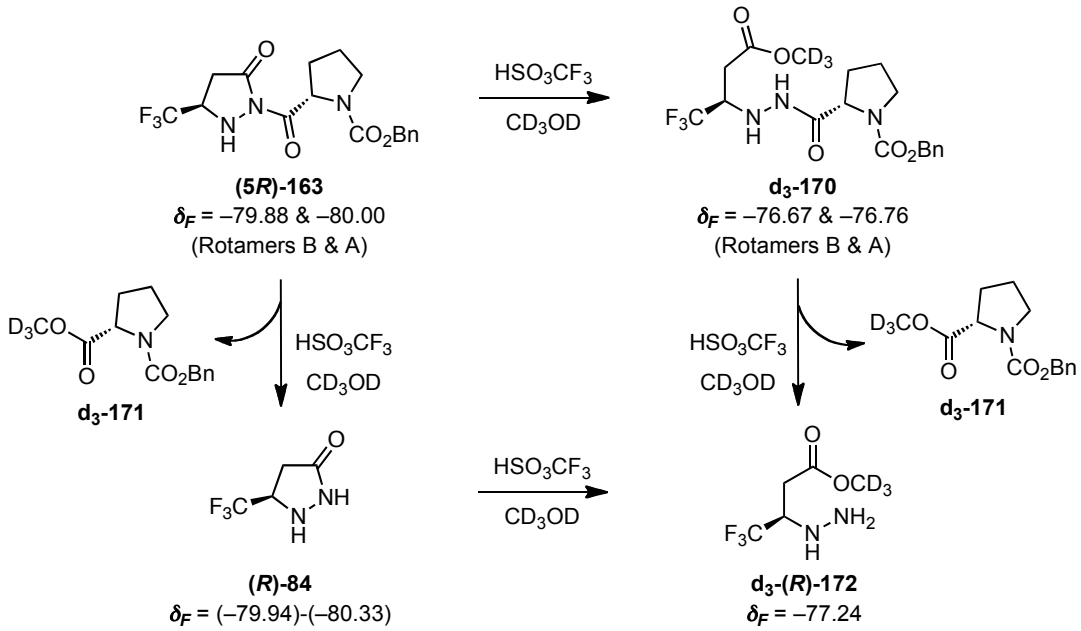
(5*R*)-163 $(CD_3)_2S(O)$)



Appendix 2: Data for ^{1}H and ^{19}F NMR spectroscopy monitoring experiments

Reactions were carried out on a a Bruker Avance 300 (282 MHz ^{19}F) or Bruker Avance 500 (500 MHz ^{1}H) spectrometer in CD_3OD. All chemical shift values are quoted in parts per million (ppm).

^{19}F NMR spectroscopic monitoring of methanolysis of catalyst (5*R*)-163



Catalyst **(5*R*)-163** (37.0 mg, 95.0 μmol) and triflic acid (0.190 M solution in CD_3OD, 0.5 mL, 95.0 μmol) were combined in an NMR tube at t = 0 and the NMR spectrometer was locked and shimmed to this solution. Reaction was monitored by ^{1}H decoupled ^{19}F NMR spectroscopy with a delay between spectrum acquisition of 30 min for the first 4.82 h and 60 min thereafter, up to 16.42 h.

Integrals were determined manually and scaled to the triflate anion peak (δ_F –80.57, integral= 1).

The chemical shift corresponding to **(*R*)-84** drifted slightly over the course of the reaction from δ_F = –79.94 to –80.33. At timepoint t = 1.28 h, this led to complete overlap of the **(*R*)-84** peak with the A rotamer of **(5*R*)-163** (δ_F = –80.00). Hence, a single integral is given for these two compounds at this timepoint.

^{19}F NMR spectroscopy integral values

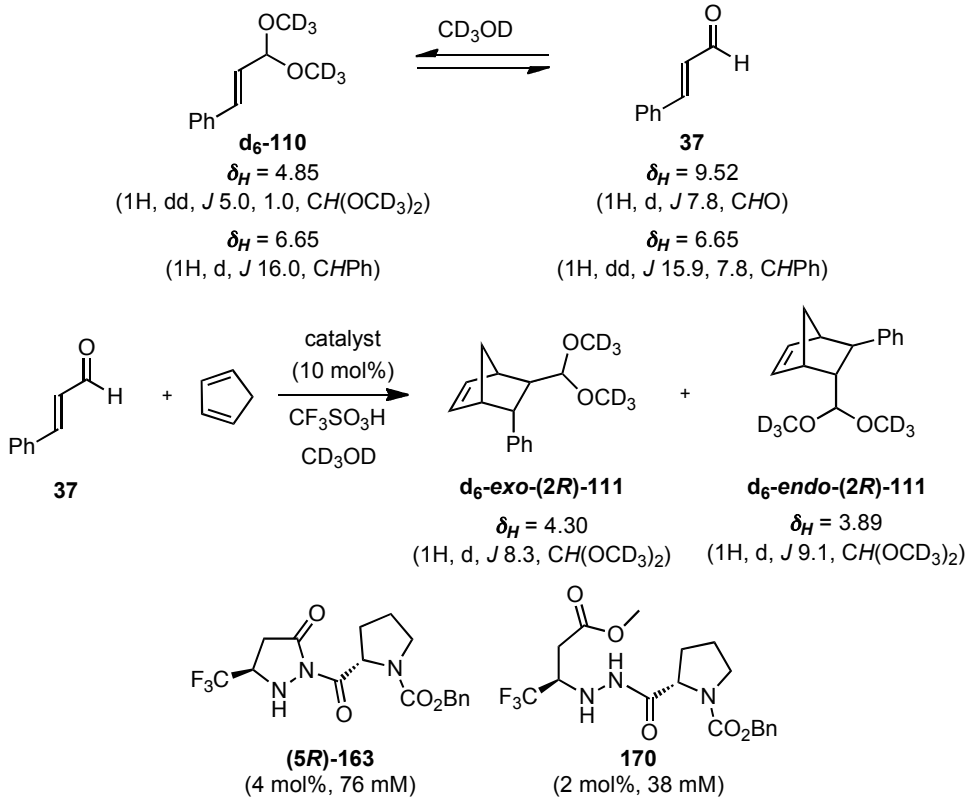
Time (h)	**170** B (-76.67)	**170** A (-76.76)	**d_3-(*R*)-172** (-77.24)	**(5*R*)-163** B (-79.88)	**(5*R*)-163** A (-80.00)	**(*R*)-84** ((-79.94)-(–80.33))	**(5*R*)-163** Total (A+B)	**170** Total (A+B)	Integral Sum
0.22	0.031	0.039	0.003	0.437	0.505	0.119	0.942	0.07	1.134
0.27	0.040	0.050	0.005	0.423	0.470	0.118	0.893	0.09	1.106
0.78	0.095	0.113	0.026	0.327	0.324	0.231	0.651	0.208	1.116
1.28	0.133	0.156	0.055	0.249	-	0.517[a]	-	0.289	1.11
1.78	0.162	0.193	0.092	0.186	0.198	0.260	0.384	0.355	1.091
2.30	0.185	0.216	0.129	0.141	0.170	0.263	0.311	0.401	1.104
2.80	0.195	0.237	0.161	0.107	0.118	0.253	0.225	0.432	1.071
3.30	0.213	0.257	0.198	0.086	0.096	0.252	0.182	0.47	1.102
3.82	0.223	0.266	0.229	0.070	0.080	0.239	0.15	0.489	1.107
4.32	0.228	0.273	0.258	0.052	0.063	0.219	0.115	0.501	1.093
4.82	0.240	0.277	0.285	0.043	0.052	0.210	0.095	0.517	1.107
5.83	0.253	0.295	0.337	0.031	0.036	0.184	0.067	0.548	1.136
6.83	0.258	0.304	0.375	0.020	0.023	0.156	0.043	0.562	1.136
7.85	0.253	0.305	0.409	0.015	0.016	0.134	0.031	0.558	1.132
8.85	0.264	0.310	0.438	0.010	0.011	0.111	0.021	0.574	1.144
9.87	0.266	0.320	0.467	0.008	0.009	0.098	0.017	0.586	1.168
10.88	0.269	0.320	0.488	0.005	0.006	0.082	0.011	0.589	1.17
11.88	0.268	0.320	0.505	0.004	0.004	0.067	0.008	0.588	1.168
12.90	0.273	0.321	0.521	0.003	0.003	0.059	0.006	0.594	1.180
13.90	0.269	0.326	0.534	0.002	0.003	0.050	0.005	0.595	1.184
14.92	0.275	0.330	0.546	0.002	0.002	0.045	0.004	0.605	1.200
15.92	0.274	0.328	0.553	0.001	0.001	0.035	0.002	0.602	1.192
16.42	0.273	0.330	0.560	0.001	0.001	0.032	0.002	0.603	1.197

a) Combined integral of **(5*R*)-163** A and **(*R*)-84**

Integral values as percentage composition

Time (h)	**170** Total (A+B)	**(5*R*)-163** Total (A+B)	**d_3-(*R*)-172**	**(*R*)-84**
0.22	6	83	0	10
0.27	8	81	0	11
0.78	19	58	2	21
1.28	26	-	5	-
1.78	33	35	8	24
2.30	36	28	12	24
2.80	40	21	15	24
3.30	43	17	18	23
3.82	44	14	21	22
4.32	46	11	24	20
4.82	47	9	26	19
5.83	48	6	30	16
6.83	49	4	33	14
7.85	49	3	36	12
8.85	50	2	38	10
9.87	50	1	40	8
10.88	50	1	42	7
11.88	50	1	43	6
12.90	50	1	44	5
13.90	50	0	45	4
14.92	50	0	46	4
15.92	51	0	46	3
16.42	50	0	47	3

^{1}H NMR spectroscopic monitoring of Diels-Alder reaction of (*E*)-cinnamaldehyde 37 and cyclopentadiene catalysed by (5*R*)-163 or 170



*Reaction with **(5R)-163***

(*E*)-Cinnamaldehyde **37** (0.120 mL, 0.950 mmol), triflic acid (76.0 mM solution in CD_3OD, 0.5 mL, 38.0 μmol), cyclopentadiene (94.0 mg, 1.43 mmol) and 1-methylnaphthalene (26.0 μL, 0.190 mmol) were combined in an NMR tube and the NMR spectrometer was locked and shimmed to this solution. Catalyst **(5*R*)-163** (4 mol%, 14.6 mg, 38.0 μmol) was added at t = 0 and reaction monitored by ^{1}H NMR spectroscopy with a delay between spectrum acquisition of 5 min for the first 17 min and 10 min thereafter, up to 256 min. Integrals were determined manually and scaled to 1-methylnaphthalene (***δ*$_H$** 7.78, integral=1).

*Reaction with **170***

(*E*)-Cinnamaldehyde **37** (0.120 mL, 0.950 mmol), triflic acid (38.0 mM solution in CD_3OD, 0.5 mL, 19.0 μmol), cyclopentadiene (94.0 mg, 1.43 mmol) and 1-methylnaphthalene (26.0 μL, 0.190 mmol) were combined in an NMR tube and the NMR spectrometer was locked and shimmed to this solution. Catalyst **170** (2 mol%, 7.90 mg, 19.0 μmol) was added at t = 0 and reaction monitored by ^{1}H NMR spectroscopy with a delay between spectrum acquisition of

5 min for the first 17 min and 10 min thereafter, up to 256 min. Integrals were determined manually and scaled to 1-methylnaphthalene (δ_H 7.78, integral= 1).

From the timepoint t = 87 min onwards, the acetal peak at δ_H = 4.85 was obscured by a peak due to residual water. Hence, integral values are given only up to this timepoint.

Reaction with ***(5R)-163*****- ^{1}H NMR spectroscopy integral values**

Time (min)	**37** (9.52)	**37**+**110** (6.65)	**110** (4.85)	***exo*-111** (4.30)	***exo*-111** (3.89)	**111 Com** (4.30+3.89)	% conversion
5	2.58	5.89	2.84	0.15	0.21	0.36	5.9
7	2.60	5.76	2.80	0.19	0.26	0.45	7.4
12	2.50	5.43	2.66	0.25	0.37	0.62	10.2
17	2.42	5.12	2.44	0.30	0.47	0.77	12.6
28	2.34	4.91	2.39	0.45	0.72	1.17	19.2
38	2.13	4.40	2.04	0.52	0.87	1.39	22.8
48	2.06	4.24	1.97	0.66	1.09	1.75	28.7
59	1.90	3.80	1.70	0.70	1.19	1.89	31.0
69	1.83	3.77	1.70	0.85	1.45	2.30	37.7
79	1.74	3.50	1.59	0.91	1.59	2.50	41.0
89	1.63	3.20	1.42	0.97	1.68	2.65	43.4
100	1.53	3.02	1.33	1.03	1.82	2.85	46.7
110	1.44	2.82	1.24	1.09	1.92	3.01	49.3
121	1.36	2.72	1.18	1.17	2.08	3.25	53.3
131	1.27	2.56	1.10	1.23	2.18	3.41	55.9
142	1.22	2.35	1.02	1.25	2.21	3.46	56.7
152	1.15	2.32	1.00	1.37	2.41	3.78	62.0
163	1.09	2.11	0.91	1.35	2.41	3.76	61.6
173	1.00	2.00	0.86	1.4	2.49	3.89	63.8
184	0.98	1.88	0.8	1.42	2.53	3.95	64.8
194	0.92	1.79	0.77	1.48	2.64	4.12	67.5
204	0.82	1.66	0.69	1.46	2.62	4.08	66.9
214	0.82	1.57	0.67	1.51	2.69	4.20	68.9
225	0.72	1.52	0.64	1.56	2.8	4.36	71.5
235	0.71	1.42	0.6	1.56	2.82	4.38	71.8
246	0.69	1.35	0.58	1.6	2.87	4.47	73.3
256	0.66	1.31	0.53	1.65	2.97	4.62	75.7

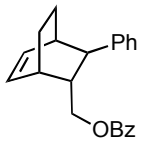
*Reaction with **170**-* ^{1}**H NMR spectroscopy integral values**

Time (min)	**37** (9.52)	**37+110** (6.65)	**110** (4.85)	***exo*-111** (4.30)	***exo*-111** (3.89)	**111 Com** (4.30+3.89)	% conversion
8	2.21	4.6	2.21	0.17	0.21	0.38	7.8
10	2.13	4.42	2.08	0.2	0.26	0.46	9.4
15	1.93	3.84	1.86	0.33	0.46	0.79	16.1
25	1.70	3.37	1.56	0.57	0.91	1.48	30.2
35	1.41	2.65	1.17	0.71	1.18	1.89	38.6
46	1.22	2.22	0.96	0.85	1.45	2.30	46.9
56	1.08	2.01	0.86	1.04	1.80	2.84	58.0
67	0.94	1.69	0.69	1.11	1.95	3.06	62.4
78	0.83	1.47	0.65	1.20	2.12	3.32	67.8
87	0.73	1.30	-	1.28	2.27	3.55	72.4
98	0.66	1.13	-	1.31	2.37	3.68	75.1
108	0.56	1.02	-	1.39	2.50	3.89	79.4
113	0.53	0.95	-	1.39	2.51	3.90	79.6
119	0.50	0.89	-	1.39	2.52	3.91	79.8
124	0.48	0.86	-	1.44	2.62	4.06	82.9
129	0.45	0.83	-	1.49	2.71	4.20	85.7
139	0.40	0.75	-	1.52	2.77	4.29	87.6
160	0.33	0.59	-	1.52	2.80	4.32	88.2
181	0.28	0.49	-	1.57	2.89	4.46	91.0
202	0.23	0.41	-	1.59	2.92	4.51	92.0
223	0.18	0.35	-	1.65	3.04	4.69	95.7
243	0.14	0.3	-	1.67	3.09	4.76	97.1
259	0.12	0.26	-	1.67	3.09	4.76	97.1

Appendix 3: HPLC chromatograms of relevant compounds

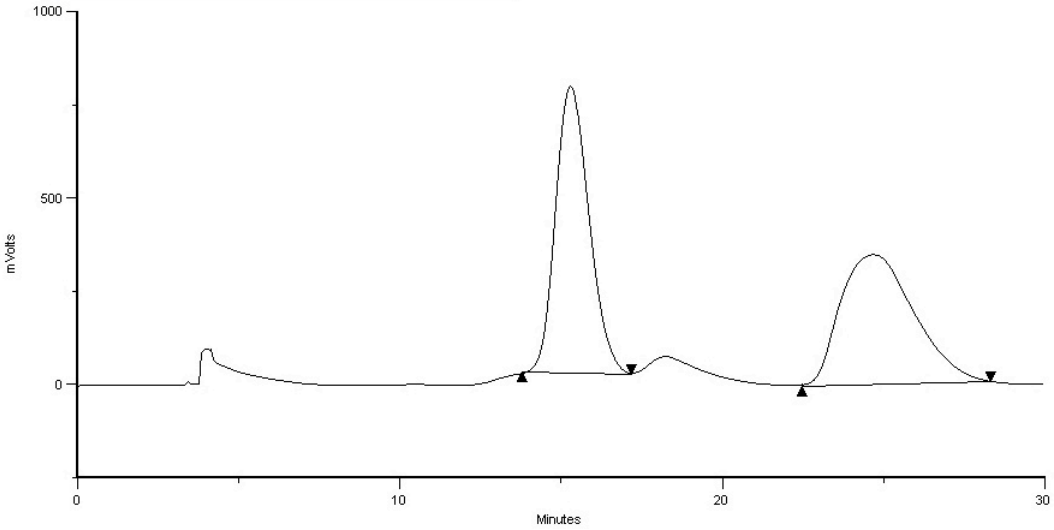
Chiral HPLC was performed on Gilson apparatus, using a ChiralPak AD-H, AS-H, OD-H, or OJ-H or IB silica column, 0.46 cm ϕ x 25 cm, using hexane and isopropanol as eluents.

endo-(1_S_,2_R_,3_R_,4_R_)-3-Phenylbicyclo[2.2.2]oct-5-en-2-yl)methyl benzoate _endo_-(2_R_)-164

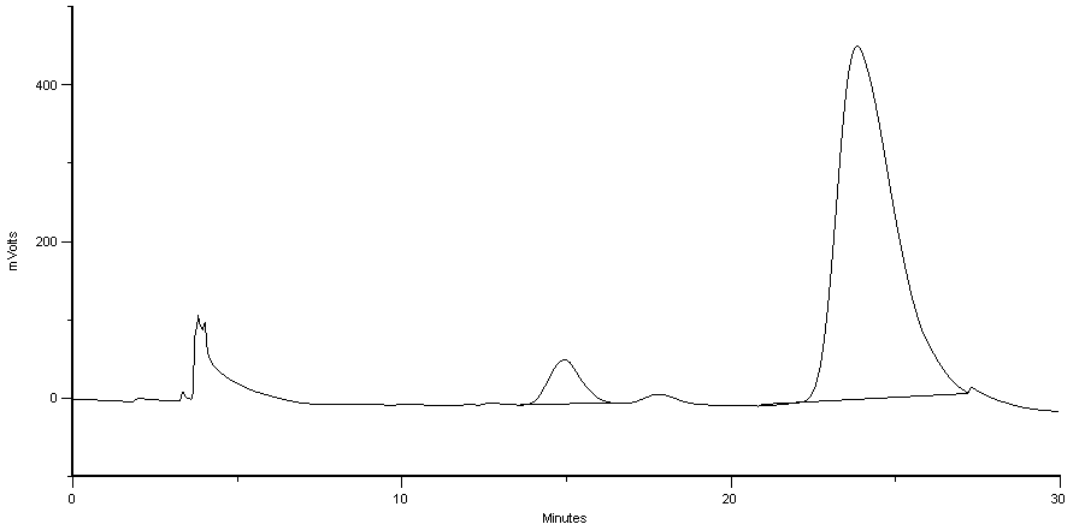


ChiralCel OJ-H column, 0.5% isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 211 nm, 85 % ee.

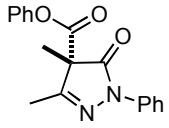
	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	15.29	3960912.00	49.95
	1.00	*2	24.68	4132192.00	50.05



	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	14.93	6887895.00	7.05
2	1.00	*2	23.83	90860744.00	92.95



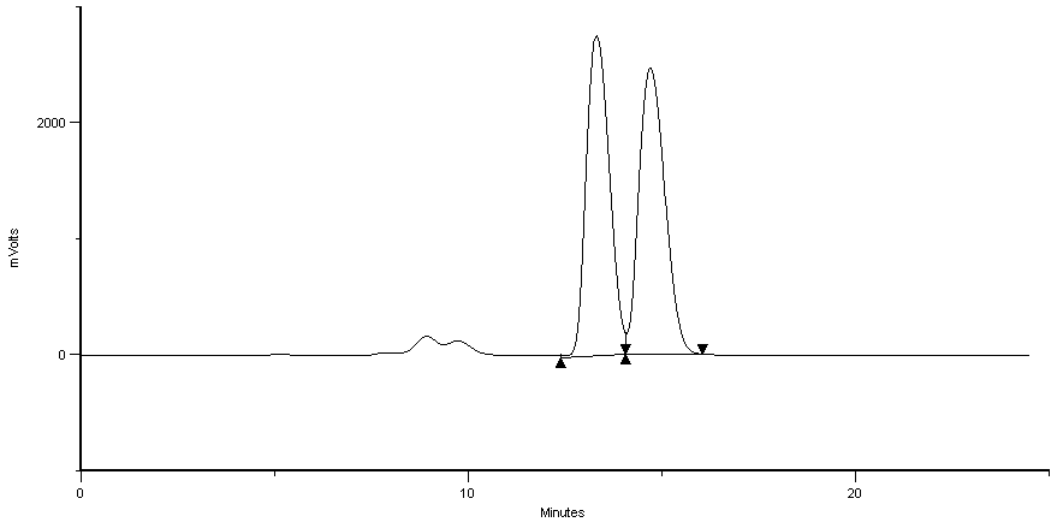
(–)-Phenyl (4,5-dimethyl-2-phenyl-5-pyrazolin-3-one)-4-carboxylate (–)-200



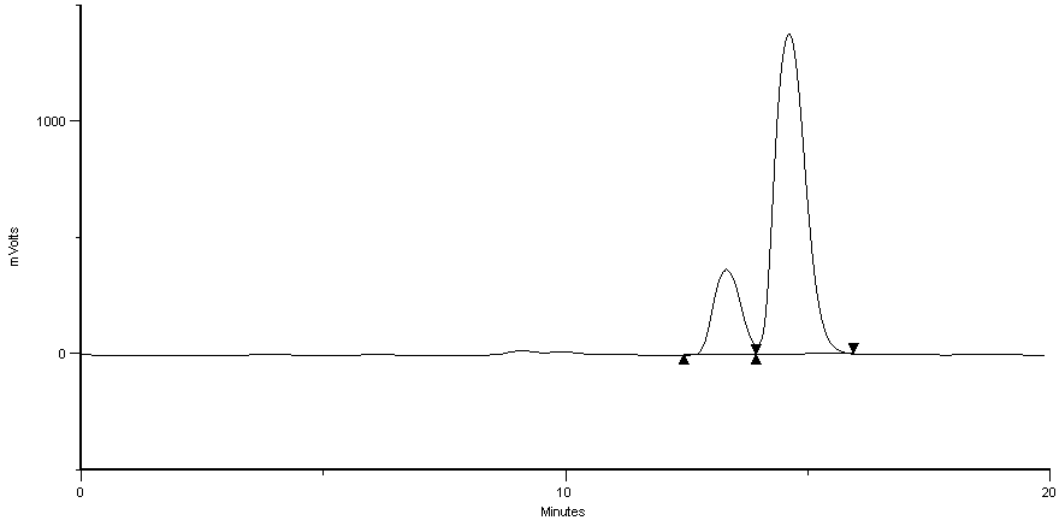
(–)-200

ChiralPax AS-H column, 1 % isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 254 nm, 62 % ee.

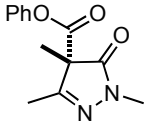
	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	13.32	93531968.0(	49.84
2	1.00	*2	14.70	94759200.0(	50.16



	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	13.33	24037918.00	19.16
2	1.00	*2	14.62	01442864.0(	80.84



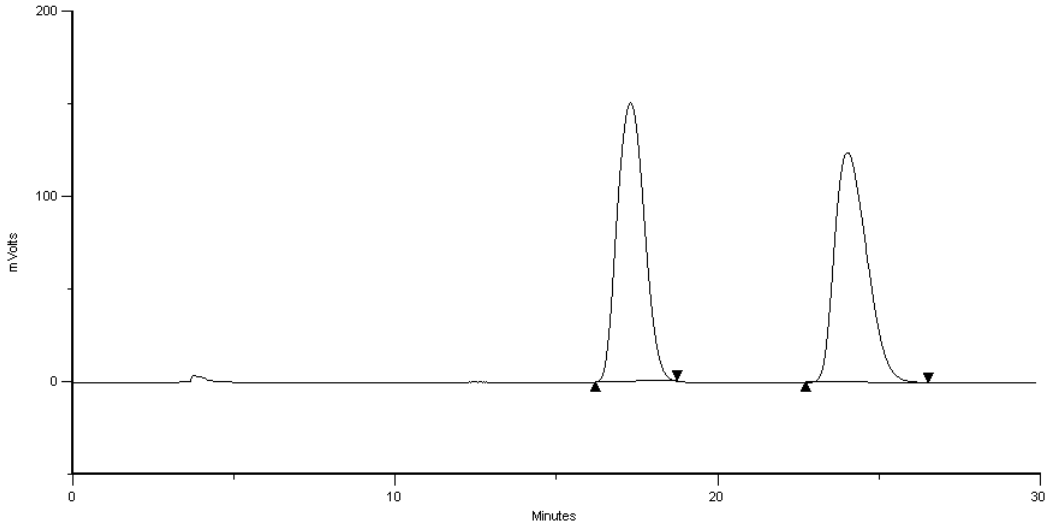
(–)-Phenyl (2,4,5-trimethyl-5-pyrazolin-3-one)-4-carboxylate (–)-211



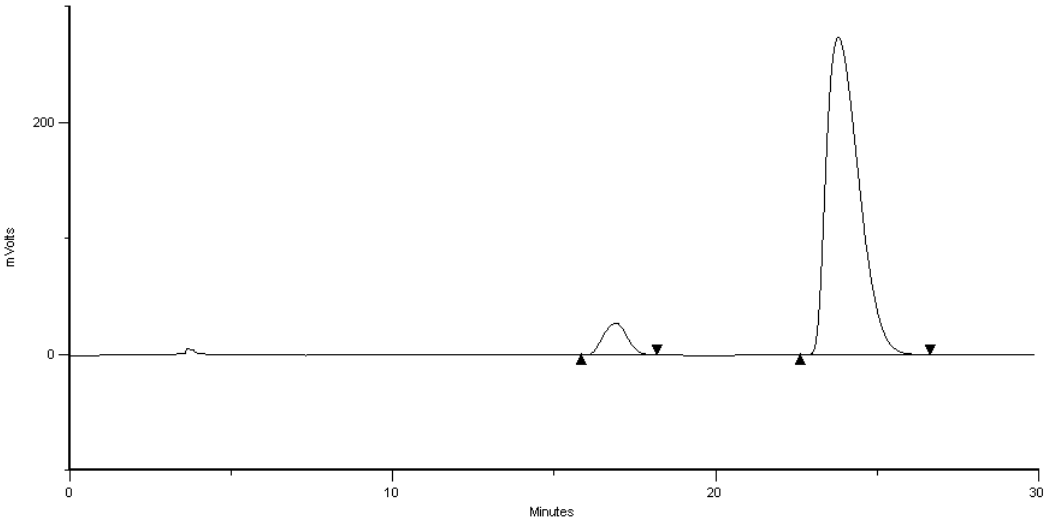
(–)-211

ChiralPax AS-H column, 1 % isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 254 nm, 86 % ee.

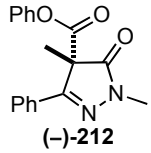
	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	17.29	4858476.00	50.43
2	1.00	*2	24.02	4607563.00	49.57



	Inj. Number	Peak Name	R. Time	Area	Area %
1	3.00	*1	16.90	2508109.75	7.20
	3.00	*2	23.80	32322304.00	92.80



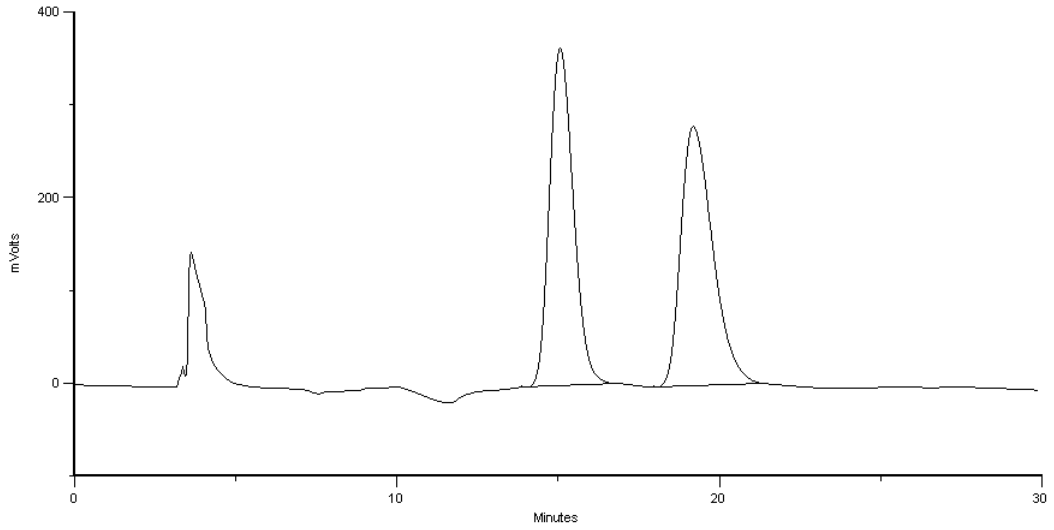
(–)-Phenyl (2,4-dimethyl-5-phenyl-5-pyrazolin-3-one)-4-carboxylate (–)-212



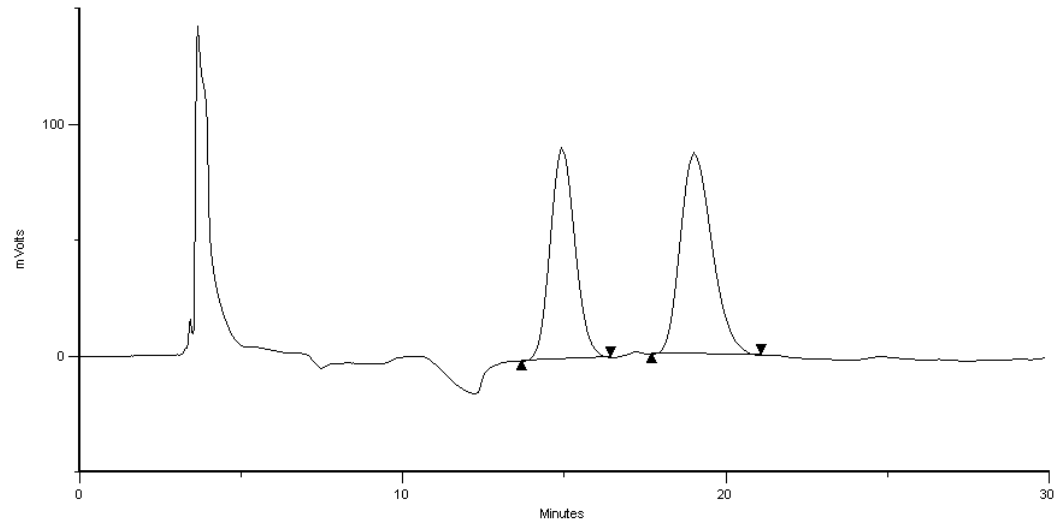
(–)-212

ChiralPax AS-H column, 1 % isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 211 nm, 10 % ee.

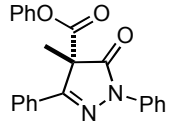
	Inj. Number	Peak Name	R. Time	Area	Area %
1	2.00	*1	15.06	31507104.00	49.36
2	2.00	*2	19.19	32319030.00	50.64



	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	14.93	8130276.00	45.05
2	1.00	*2	19.01	9915204.00	54.95



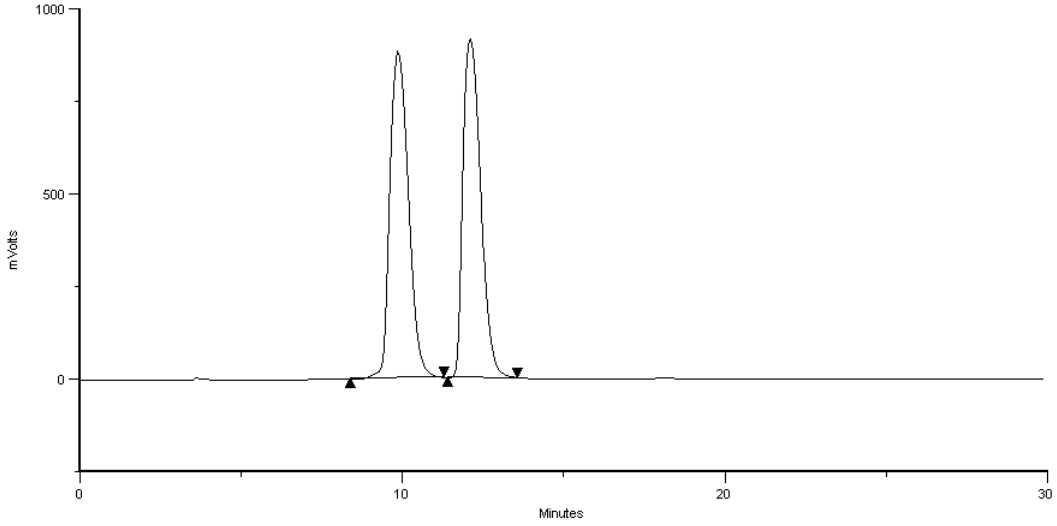
(+)-Phenyl (4-methyl-2,5-diphenyl-5-pyrazolin-3-one)-4-carboxylate (+)-213



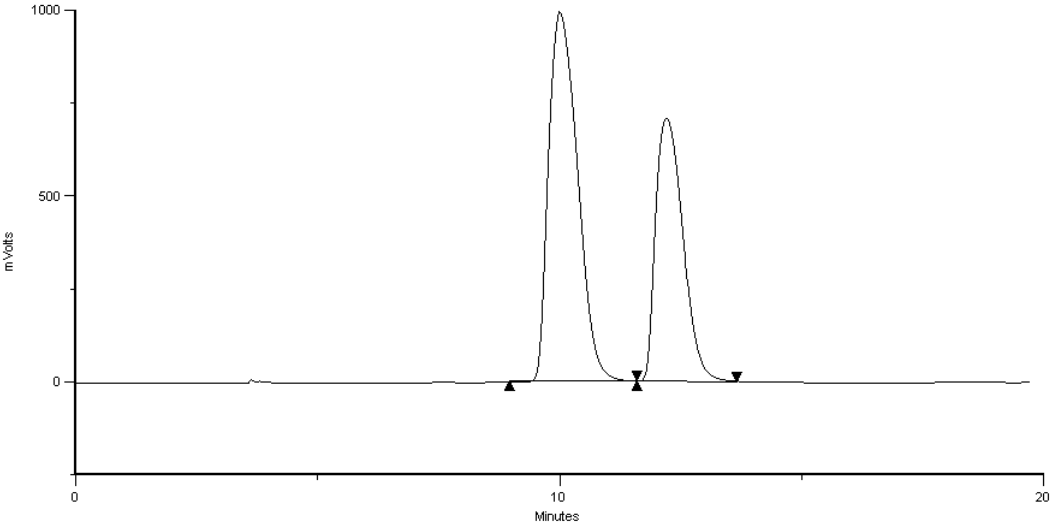
(+)-213

ChiralPax IB column, 1 % isopropanol:hexane, flow rate = 1.0 mL min^{-1}, 254 nm, 20 % ee.

	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	9.86	59293600.00	50.01
2	1.00	*2	12.10	59268248.00	49.99



	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	10.01	59365312.00	59.57
	1.00	*2	12.21	47076728.00	40.43



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[39] In the rest of this report, chiral bicyclic Diels-Alder adducts will be differentiated by their 2-position stereochemistry only e.g. ***exo*-(1*R*,2*R*,3*R*,4*S*)-38** will be referred to as ***exo*-(2*R*)-38**.

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